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Controlling Cadmium in the Human Food Chain
A Review and Rationale Based on Health Effects

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16. ABSTRACT

Cadmium can cause acute and chronic illness in humans. The evidence for inclusion of Cd among the elements known to be human carcinogens is insufficient. There is scientifically recognized agreement that renal tubular damage and pulmonary emphysema are the two cardinal pathological lesions associated with excessive Cd exposure. Renal tubular damage is the chronic effect attributed to environmental Cd exposure for the nonoccupationally exposed population. For the nonoccupationally exposed population the primary routes of Cd exposure are through food and tobacco smoke. Most persons are in an approximate Cd balance and tend to accrete Cd until approximately age 50, after which a negative balance ensues. Cadmium is accumulated in the renal cortex and concentrations of between 200 and 300 μg/g wet wt generally result in renal dysfunction, with the 200 μg/g level being the most widely accepted number at which the first signs of β_2-microproteinuria occur. In the United States the current mean level of Cd in the kidney cortex is 20–35 μg/g with about 0.6% of the population exceeding 100 μg/g. The impact of increasing soil Cd on the movement of Cd from soil to plant to animal to human would indicate little reason for concern. In contrast, the movement of Cd from soil to plant to human can be of concern. The degree of risk is dependent upon the amount of the diet which is affected, diet selection of the individual, soil pH at which the crop is produced, and the amount of Cd added to the soil.

Contents. Introduction. Environmental Exposure. Pharmacokinetics. Health Effects. Acute health effects. Chronic health effects. Mutagenic properties of Cd. Tumorigenic properties of Cd. Carcinogenesis in man. Renal effects. *Dose–Effects/Dose–Response Relationships.* Dose–effect relationships. Dose–response relationships. Population at risk. Maximum allowable exposure. *Current Risk Evaluation.* Diet. Soil–plant response. Relationship between crop response and diet. Calculation of sludge-loading rates.

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Controlling Cadmium in the Human Food Chain: A Review and Rationale Based on Health Effects

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Cadmium can cause acute and chronic illness in humans. The evidence for inclusion of Cd among the elements known to be human carcinogens is insufficient. There is scientifically recognized agreement that renal tubular damage and pulmonary emphysema are the two cardinal pathological lesions associated with excessive Cd exposure. Renal tubular damage is the chronic effect attributed to environmental Cd exposure for the nonoccupationally exposed population. For the nonoccupationally exposed population the primary routes of Cd exposure are through food and tobacco smoke. Most persons are in an approximate Cd balance and tend to accrete Cd until approximately age 50, after which a negative balance ensues. Cadmium is accumulated in the renal cortex and concentrations of between 200 and 300 μg/g wet wt generally result in renal dysfunction, with the 200 μg/g level being the most widely accepted number at which the first signs of β_2-microproteinuria occur. In the United States the current mean level of Cd in the kidney cortex is 20–35 μg/g with about 0.6% of the population exceeding 100 μg/g. The impact of increasing soil Cd on the movement of Cd from soil to plant to animal to human would indicate little reason for concern. In contrast, the movement of Cd from soil to plant to human can be of concern. The degree of risk is dependent upon the amount of the diet which is affected, diet selection of the individual, soil pH at which the crop is produced, and the amount of Cd added to the soil.

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INTRODUCTION

Recent encouragement by the U.S. Environmental Protection Agency and the Congress to find more cost-effective and environmentally acceptable means for treatment and disposal of municipal wastes has led to an intensive evaluation of the practice of disposal of sludge from municipal wastewater treatment plants on land. This practice provides nutrients to the soil and at the same time solves a disposal problem. With increasing amounts of sludge being applied to land, questions have arisen concerning the potential for metals to pass through the human food chain. Cadmium is the metal considered most likely to cause problems and hence may need to be limited (Pahren *et al.*, 1979).

In this review, a procedure is presented for calculating the amount of Cd that could pass through the food chain from sludge to man. Only an overview is

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presented on exposure and health effects since several others have treated these subjects in a more comprehensive manner (e.g., Friberg *et al.*, 1974). Discussion of occupational and inhalation exposure is intentionally very limited. The literature on the passage of Cd through soil–plant systems is summarized and the more thorough reviews are cited. Finally, data are presented which relate Cd-containing sludge application rates to population exposure through the food chain under several optional agricultural management systems. These results will permit decision makers to select the conditions and constraints for sludge application.

ENVIRONMENTAL EXPOSURE

The major nonoccupational routes of human Cd exposure are through food and tobacco smoke. Data published by the U.S. Food and Drug Administration (Compliance Program Evaluation, 1974), based on market basket surveys over 7 years, showed that the mean Cd intake of 15- to 20-year-old males in the United States, including Cd from water, was 38 ± 12 μg/day. Teenage males had the highest per capita food intake of any group within our population, but their diet may or may not be representative of Cd-rich foods. As can be readily seen (Fig. 1), there is no apparent trend for dietary Cd intakes over the 7 years. The range from 26 to 51 μg/day intake illustrates the degree of variability that exists in estimates among the years. Additionally, in 1974, FDA surveyed the Pb–Cd–Zn content of 32 adult foods (71 samples of each food). By using the median findings in those surveyed foods a daily intake from food of 33 μg was calculated for teenage males. This agrees quite well with the 38 μg/day 7-year mean. However, when the mean findings were used, the calculated daily intake was 72 μg. This discrepancy, between mean and median value, would imply that the distribution was not normal but was substantially skewed.

When evaluating data on metals in food, the detection limits should be kept in mind. For Cd, the minimum quantitation level was 20 ppb during those years

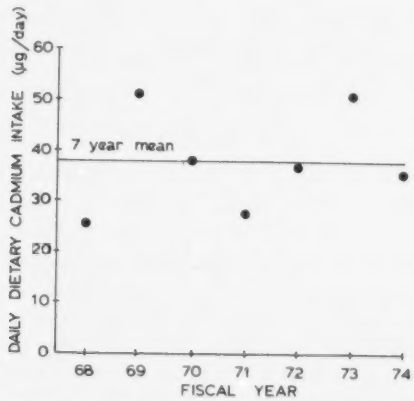

FIG. 1. Daily cadmium intake in the total diet of 15- to 20-year-old males (Compliance Program Evaluation, 1974).

(Mahaffey *et al.*, 1975). Food samples in the market basket survey were generally near the limit of detection. An alternate procedure for determining Cd intake is to find the Cd concentration in feces and calculate the intake from an absorption factor. Fecal concentrations are much higher and well within the sensitivity of analytical procedures. Table 1 shows the results of three studies sponsored by EPA using this estimation method. The gastrointestinal absorption factor used was 4.6% (McLellan *et al.*, 1978). The Cd intake values are about half the level found using the market basket approach. It is important to note the individual variations in ingestion levels observed; that is, approximately 5% of the study population appear to exceed 30–40 μg Cd/day intake, and 1% exceed 50 μg Cd/day intake (Table 1). However, since individuals were not repeatedly sampled, it should not be assumed that the same 1% of the population regularly ingests over 50 μg daily.

Adjustment of the 38 μg/day intake rate by the recommended daily calorie intake for various age groups results in an average daily Cd intake from birth to age 50 of 33 μg/day for men and 26 μg/day for women. However, data based on fecal excretion gives intake figures of 18 and 21 μg/day for teenage males residing in Dallas (Kjellström, 1979) and Chicago (Kowal *et al.*, 1979), respectively.

The data in Table 2 indicate that the daily intake of Cd via food for individuals living in the United States is comparable to that in other countries.

Cadmium is selectively concentrated by certain food crop classes. In particular, root crops and leafy vegetables are more responsive to soil Cd. Their Cd content depends to a high degree on the soil solution concentration of the element (Street *et al.*, 1977). Municipal sludges, containing high levels of Cd of industrial origin, applied to agricultural lands as fertilizer are potentially important sources of Cd entry into the human food chain (CAST, 1976). To date, however, there have been no documented occurrences of Cd toxicity in animals or man attributed to direct consumption of vegetation grown on land treated with municipal sludge (Garrigan, 1977). Wastewater containing Cd used to irrigate fields producing crops for human consumption may impact dietary levels. The widespread use of phosphate fertilizers, most of which contain significant amounts of Cd (EPA, 1975a), could ultimately increase the amount of Cd in the diet.

Aquatic food species, including fish, crabs, oysters, and shrimps, bioconcentrate Cd, as do visceral meats (liver, kidney, pancreas). Cadmium content de-

TABLE 1
DISTRIBUTION OF DAILY CADMIUM INTAKE (μg/day) USING FECAL EXCRETION PROCEDURE[a]

Study	*N*	Percentage of population which exceed displayed μg/day value			
		50	10	5	1
Chicago 1974	192	13.7	26.4	31.9	45.3
Chicago 1976	199	9.1	28.3	39.1	71.9
Dallas 1975	86	12.5	21.6	25.3	33.8

[a] Adapted from Kowal *et al.* (1979).

TABLE 2
DAILY CADMIUM INTAKE FROM FOOD

Country	μg/day	Reference
United States	38	Compliance Program Evaluation (1974)[a]
Canada	52	Kirkpatrick and Coffin (1977)
West Germany	48	EPA (1975b)
Rumania	38–64	EPA (1975b)
Czechoslovakia	60	EPA (1975b)
Japan (unpolluted areas)	59	EPA (1975b)
Sweden	16–19	Kjellström *et al.* (1978)
Australia	30–50	Miller *et al.* (1976)
New Zealand	21–27	Guthrie and Robinson (1977)
United Kingdom	15–35	Drury and Hammons (1978)

[a] This estimate is the mean of 7 years of data from the FDA's Total Diet Study. Individual year's estimates ranged from 26 to 51 μg/day.

pends on the age of animals at slaughter, older animals having higher concentrations (Kreuzer *et al.*, 1976; Nordberg, 1974). Although numerous studies have reported only inconsequential accumulation of Cd by muscle tissue, it should be noted that poultry fed Cd-supplemented diets have been reported (Leach *et al.*, 1979) to concentrate Cd in muscle by a factor of 2–43 times control levels, depending upon the concentration of Cd in the diet and the duration of the experiment. Remarkably, little Cd was found in eggs even at the highest dosage level. While oysters and crustaceans may concentrate Cd to a factor of 3×10^5, there is no evidence that the element bioaccumulates in marine food chains (Fassett, 1975).

Milk is an important source of Cd to the infant and child. Breast milk has been shown to have a median Cd content of 11. 1 μg/liter (Pinkerton *et al.*, 1972). An extensive sampling of cow's milk has also been carried out involving multiple samples collected over a 2-year period from each of the 48 contiguous states and the District of Columbia (Pinkerton *et al.*, 1971). Cadmium values were found to range from 17 to 41 μg/liter with a median value of 26. Intracity variations were noted to be almost as large as intercity variations. The higher levels of Cd in bovine milk compared with human milk parallels the pattern observed for most minerals and trace elements. Milk intake in the infant averages from about 350 ml/day at birth to a maximum of about 840 ml/day at 2 months, where it plateaus, due to the introduction of increasing amounts of solid foods into the diet.

Based upon an average duration of breast feeding per lactation of 7 months, Pinkerton *et al.*, (1972) calculated that the average infant will ingest 1699 μg of Cd if breast fed over this period and 3700 μg if fed cow's milk. Milk accounts for approximately half the Cd ingested during the first year of life in bottle-fed babies compared to approximately one-fourth for breast-fed infants.

Tobacco in all its forms contains appreciable amounts of Cd. Since the absorption of Cd from the lung occurs at a substantially higher rate than that from the gastrointestinal tract, smoking contributes significantly to total body burdens. American cigarettes have been found to contain 1.5 to 2.0 μg per cigarette (Men-

den *et al.*, 1972) and about 70% of this passes into the smoke (Nandi *et al.*, 1969). All data agree that 0.1 to 0.2 μg Cd are inhaled for each cigarette smoked. Thus, smoking 20 cigarettes per day will result in the inhalation of about 3 μg/day. Because inhaled Cd is absorbed more readily (assuming 40%), this is equivalent to ingesting 25 μg from food. Using *in vivo* neutron activation analysis Ellis *et al.*, (1979) have reported that 1.9 μg of Cd is actually absorbed for each pack of cigarettes smoked. This also implies that absorption from the respiratory tract may exceed 60%. It has been pointed out that workers handling Cd compounds may contaminate their cigarette or pipe tobacco and further augment the high metal load contributed by smoking (Piscator *et al.*, 1976).

Ambient air is not a significant source of Cd for the vast majority of the United States population. Data from the National Air Sampling Network have been summarized by Tabor and Warren (1958) and Schroeder (1970). Data collected in 1966 in 58 urban and 29 nonurban areas showed a range of concentrations of 2–370 and 0.4–26 ng/m^3, respectively. The data emphasize that nearly all airborne Cd is due to man's activities. Highest concentrations are consistently found in industrialized cities and in the vicinity of smelting operations (Fleischer *et al.*, 1974). In areas where there are no such sources of airborne Cd pollution, the levels observed have generally been around 0.001 μg/m^3, which leads to an average inhaled amount of approximately 0.02–0.03 μg/day for adults. In those cities with the highest levels of Cd air pollution, i.e., those having excursions to approximately 400 μg/m^3, the maximum amount inhaled could rise in extreme occasion to 8.0 μg/day. Regulation of certain industrial sources of airborne Cd is currently under consideration by the Office of Air, Noise and Radiation, EPA.

Drinking water also contributes relatively little to the average daily intake. A survey of 969 U.S. community water supply systems (McCabe *et al.*, 1970), representing 5% of the national total, revealed an average Cd concentration of 1.3 μg/liter. Only three systems exceeded concentrations of 10 μg/liter. Of 2595 distribution samples taken during this same survey, only four samples exceeded the 10 μg/liter standard and the maximum sample had a concentration of 110 μg/liter. Apparently, an occasional water source is acidic enough to cause some dissolution of metal from distribution piping, i.e., galvanized pipe. Most analyses of seawater have reported average concentrations of 0.1 to 0.15 μg/liter (Fleischer *et al.*, 1974). Since this is less than that of freshwater sources entering the sea and far below the levels expected from solubility factors, it has been suggested that Cd is effectively removed by coprecipitation with or adsorption on clays, hydrous manganese oxides, or phosphorites (Posselt, 1971). On the basis of the above community water supply study and an average adult consumption rate of 2 liters/day, drinking water sources probably contribute not more than 3 to 4 μg/day to the average total Cd intake.

PHARMACOKINETICS

While ingestion constitutes the major part of human Cd intake, only a small proportion, i.e., approximately 4.6 ± 4% is absorbed, and the rest passes directly into the feces. Gastrointestinal absorption is influenced by a number of dietary

factors. Diets low in Ca lead to significantly higher levels of absorption and deposition of Cd into intestinal mucosa, liver, and kidneys (Washko and Cousins, 1976), and corresponding decreases in fecal excretion. Diets deficient in Vitamin D also lead to increased Cd absorption (Worker and Migicovsky, 1961). In addition, low-protein diets lead to considerably higher levels of Cd in various organs, irrespective of the Ca content of the diet (Suzuki *et al.*, 1969). Gontzea and Popescu (1978) have demonstrated that the quantity and quality of dietary protein significantly affects Cd toxicity. Similarly, deficiencies of Zn, Fe, and Cu have been shown to enhance Cd uptake and subsequent adverse effects (Banis *et al.*, 1969; Bunn and Matrone, 1966; and Hill *et al.*, 1963). Ascorbic acid deficiency also promotes Cd toxicity (Fox and Fry, 1970). The complex relationship between Cd and various heavy metals and nutrients has been reviewed by Bremner (1979).

Human studies using ^{115m}Cd given orally have yielded absorption values of 6 (range 4.7–7.0%) and 4.6% (range of 0.7–15.6%) (Rahola *et al.*, 1972; McLellan *et al.*, 1978). In the latter study, total body counting was used to determine Cd absorption in 14 healthy subjects aged 21–61 years. A trivalent Cr ($CrCl_3$) marker, which is poorly absorbed from the gastrointestinal tract, was given along with ^{115m}Cd, assuming that unabsorbed Cd would have the same transit time as Cr. The average body retention of radio Cd determined between 7 and 14 days after the disappearance of the Cr marker from the body was 4.6%, with a standard deviation of ±4%. Various animal experiments have usually given lower oral absorption figures, i.e., approximately 2%, for ingested Cd (Friberg *et al.*, 1974).

In contrast to ingestion, a relatively large proportion of respired Cd is absorbed and inhalation represents a major mode of entry into the body for smokers and occupationally exposed persons. The fate of inhaled Cd, in common with other respirable pollutants, depends upon particle size, solubility, and lung status. When a large proportion of particles are in the respirable range and the compound is relatively soluble, 25% of the inhaled amount may be absorbed. Cadmium fume may have an absorption of up to 50%, and it is estimated that up to 50% of Cd in cigarette smoke may be absorbed (Friberg *et al.*, 1974; Elinder *et al.*, 1976). The work of Ellis *et al.*(1979) suggests that up to two-thirds of Cd in cigarette smoke may be absorbed. Retrograde movement of particulate Cd due to mucociliary transport may lead to eventual swallowing and gastrointestinal tract absorption.

Irrespective of the route of entry, Cd is principally stored in the liver and kidneys, with higher levels initially found in the liver (Gunn and Gould, 1957; Kanwar *et al.*, 1980). Following single exposures, relocation occurs and liver concentrations eventually are exceeded by those of the renal cortex. Repeated exposures result in eventual high concentrations in both organs. Continued excessive exposure eventually leads to a level of about 200–300 mg/kg wet wt in the renal cortex. After this pathological changes occur, resulting in an increased excretion of Cd and protein in the urine, and no further accumulation occurs (WHO Task Group, 1977). The accumulation in the liver and kidneys seems to be mainly dependent on the storage of Cd in association with the Cd-binding protein, metallothionein (Friberg *et al.*, 1974; Chen *et al.*, 1975; Nordberg and Nordberg, 1975).

Cadmium, unlike many trace metals, has no known function in normal metabolic processes. The factor which makes Cd contamination of the environment a particularly serious hazard, from the human health standpoint, is its pronounced tendency to accumulate in biologic tissue. Elinder and Kjellström (1977) have compared renal Cd levels in specimens taken in recent autopsies with specimens collected in the last century. These data indicate that Cd body burdens are increasing, perhaps reflecting increased general environmental exposure to the element. A review of a great number of studies indicates that the total body burden of Cd in humans increases with age (Friberg *et al.*, 1974) from very minimal levels at birth (<1 μg) (Henke *et al.*, 1970) to an average of up to 30–40 mg by the age of 50 in nonoccupationally exposed individuals (Friberg *et al.*, 1974). About 50% of this accumulation is found in the kidneys and liver. The kidneys contain approximately one-third of the average body burden with the highest levels localized in the renal cortex. In general, the liver continues to concentrate Cd until the late decades of life, while kidney concentrations increase to the fourth decade, peak, and steadily decline from the sixth decade (Gross *et al.*, 1976; Spickett and Lazner, 1979). The observed decline in kidney Cd concentrations after age 50 has been attributed to age-dependent changes in food intake, decreased smoking, cohort-related exposure variations, decreased survival of persons with high renal concentrations, and increased excretion in older persons. Travis and Haddock (1980) have concluded that age-dependent renal changes are the most plausible explanation. The pancreas and salivary glands also contain considerable concentrations of Cd, while the brain and bone acquire only very small quantities (Nordberg, 1974). Smokers have an appreciably greater body burden of Cd than nonsmokers. The average concentration in the renal cortex is approximately doubled in smokers (Hammer *et al.*, 1973; Elinder *et al.*, 1976; Ostergaard, 1977; Kjellström, 1979). Kjellström reportes kidney cortex values for U.S. nonsmokers to be 12 μg/g, while those for smokers are 24 μg/g (Kjellström, 1979). Ellis *et al.* (1979) reported values of 3.1 mg total kidney burden for nonsmokers and 5.8 mg for smokers. Values for the liver were 2.3 and 4.1 μg/g for the nonsmoker and smoker, respectively.

Blood levels in newborn babies are correlated with maternal blood levels, but average only 50% of the maternal levels (Lauwerys *et al.*, 1978). In environmentally exposed children, urinary Cd levels were a more sensitive indicator of exposure than blood Cd (Roels *et al.*, 1978b). Lauwerys *et al.* (1979b), who studied newly Cd-exposed workmen, found that after initial exposure blood Cd increases for approximately 120 days before plateauing. In nonoccupationally exposed persons, the mean level of Cd in the blood is usually less than 1 μg/100 ml. Persons without known exposure, aged 2 months to 31 years (average 4.9 years), are reported as having slightly lower levels, i.e., 0.66 μg/100 ml (Smith *et al.*, 1976). Smokers are reported as having blood Cd levels 50% greater than nonsmokers (Zielhuis *et al.*, 1977).

Several reports indicate that urinary excretion of Cd is approximately 1–2 μg/day in the general population (Imbus *et al.*, 1963; Szadkowski *et al.*, 1969). There is a modest increment in urinary levels with age (Katagiri *et al.*, 1971;

Kowal *et al.*, 1979). Urinary excretion may be markedly elevated in exposed workers, including those without renal damage (Friberg *et al.*, 1974). Urinary Cd levels have been found to increase rapidly to a value of about 15 μg/g creatinine, which is followed by a second phase between the 15th and 120th day of exposure in which the level increases more slowly (Lauwerys *et al.*, 1979b). After 120 days there is again a very rapid rise in urinary Cd. The authors propose a tentative biologic threshold of 10 μg Cd/g creatinine for occupationally exposed adult males. If renal tubular dysfunction should occur due to Cd accumulation, the rate of urinary Cd excretion will further increase. This, in turn, can result in a considerable decrease in renal Cd levels (Kjellström, 1976). It should be mentioned that average renal tissue levels fall after age 50, even in "normal" persons showing no symptoms of Cd-induced renal disease.

Bernard *et al.* (1980) have studied blood and urine levels of Cd in rats receiving either long-term intraperitoneal or oral Cd. In animals receiving 2, 20, and 200 ppm of Cd the blood Cd concentration increased to plateau values after about 3 months and was proportional to the concentration in drinking water. It was, therefore, considered to be a reflection of recent exposure. The Cd concentration in urine fluctuated more than that in the blood, but at all doses, and before renal damage occurred, the amount excreted tended to increase with treatment duration. The significant correlation between the Cd level in the renal cortex and the level in the urine may confirm that urinary Cd is mainly a reflection of body (renal) burden. This was consistent with epidemiological investigations (Lauwerys *et al.*, 1979a) and with studies in Sweden (Elinder *et al.*, 1978).

Fecal excretion appears to reflect the dietary intake closely (Tipton and Stewart, 1970; Kojima *et al.*, 1977), as might be anticipated from the previously discussed absorption data. Smokers have a slightly increased fecal excretion rate, the increase averaging 3.2 μg/day (Kjellström *et al.*, 1978). It is not known how much fecal Cd may be derived from intestinal epithelium or biliary excretion. Saliva contains up to 0.1 μg/g Cd (Dreizen *et al.*, 1970) and may contribute significantly to fecal excretion, since a normal adult will secrete 1000–1500 ml/day. The amount of gastrointestinal reabsorption is unknown. Biliary excretion has been studied by Stowe (1976), who observed normal rat bile to contain 22 ± 3 μg/kg. Rats fed 100 ppm Cd excreted bile containing 50 ± 6 μg/kg.

Hair is a minor excretory pathway and may contain from 0.5 to 3.5 μg/g (Friberg *et al.*, 1974). In infancy, human hair has been shown to have relatively high levels of Cd, which decline thereafter throughout life (Gross *et al.*, 1976). While positive correlations have been reported between environmental levels (Hammer *et al.*, 1971) and occupational exposure and visceral organ levels (Oleru, 1975), these associations are generally too week to permit accurate quantitative assessments of human exposure to Cd by means of hair analyses. Kowal *et al.* (1979) reported negative correlations between hair Cd and Cd levels in urine and blood.

Human milk may be regarded as a minor excretory mechanism for Cd, as well as a source of intake for breast-fed infants. Breast milk has been found to have a median Cd content of 11.1 μg/liter (range 8.8–134) based on 23 samples collected from 14 subjects (Pinkerton *et al.*, 1972). Since lactation averages 7 months in

those women electing to breast feed, this group has estimated that an average of 1699 μg of Cd is secreted per lactation. Levels were not higher in smokers.

Estimates of whole-body biologic half-time of absorbed Cd have been derived in a number of ways. Direct comparison of urinary excretion levels and estimated body burden have been performed using Japanese, American, and German data (Friberg *et al.*, 1974). These data suggest a half-time of 13 to 47 years. Using *in vivo* neutron activation analysis, Ellis *et al.* (1979) derived a biologic half-time for the whole body of 15.7 years with a range of 10–33 years. Similar time frames have been found using more complex metabolic models. Friberg *et al.* (1974) concluded that the biologic half-time is probably 10 to 30 years. These methods suffer the disadvantage that actual body burdens cannot be ascertained for the living subject, and are assumed to be the same as averages derived from autopsy studies.

Only two human studies using radioisotopes are available. Rahola *et al.*, (1972) stated that it was not possible to accurately determine a biologic half-time, but provided a shortest estimate of 130 days and a longest of infinity. In a single human subject for whom the figure could be calculated, the biologic half-time was 100 days (McLellan *et al.*, 1978).

From the foregoing, it is obvious that the data are not in good agreement regarding Cd half-time, with estimates varying at least 100-fold (months vs decades). Since this is a critical issue in terms of maximum daily limits, it is essential that more new data be generated to resolve this facet of Cd metabolism. Nomiyama *et al.* (1979) have demonstrated in Rhesus monkeys that Cd half-time is inversely related to the oral intake of the element. This may explain some of the wide variation seen in human studies.

In summary, from the exposure, intake, absorption, and excretion data it appears that most persons are in an approximate Cd balance. That is, they excrete Cd at almost the same rate it is absorbed. Autopsy data demonstrate a tendency to accrete Cd until approximately age 50, after which a negative balance ensues. The reasons for this decline are unknown. It is unrelated to the presence or absence of renal disease, but may be due to age-dependent renal changes (Travis and Haddock, 1980). It has also been suggested that the observed decrease may be an artifact, related to the possibility that older persons may have been exposed to far lower Cd levels during their youth (Hammer *et al.*, 1973).

HEALTH EFFECTS

Extensive information exists on the acute and chronic effects of Cd in man and experimental animals. Much of the data on animals, however, is derived from studies utilizing relatively high exposures to Cd administered by parenteral injections. Such data, while often of questionable environmental relevance, are valuable in delineating the upper range of toxicological effects in a number of organ systems. Of much more crucial importance for present purposes are studies which investigate adverse health effects associated with chronic exposures at lower, enviromentally encountered Cd levels.

Acute Health Effects

Adverse health effects observed in experimental animals at high Cd exposure levels include serious acute damage to several different organ systems. Included among the acute, high-exposure effects are morphological or functional signs of: injury to the pulmonary tract, testicular necrosis, embryotoxic and teratogenic responses, endocrine system derangement, experimental hypertension and related cardiovascular responses, anemia, hepatotoxicity, tumorigenesis, mutagenesis, and reduced immunological responses. Such effects have been most consistently demonstrated to occur after single intraperitoneal or subcutaneous injections of various Cd salts in solution, and at dose levels exceeding 0.5–1.0 mg Cd/kg body wt.

Relatively few of the above acute effects, however, have been demonstrated to occur via environmentally relevant routes of exposure, either for animals or man, even at high exposure levels. About the only exception to this is the induction of respiratory tract damage with occupational exposures.

Symptoms from acute poisoning by Cd oxide fumes appear 4 to 6 hr after exposure and include cough, shortness of breath, and tightness of the chest. Pulmonary edema may ensue within 24 hr, often to be followed by bronchiopneumonia. Most cases are resolved within a week. The fatality rate ranges between 15 and 20% (Bonnel, 1965). Latter effects from acute overexposure include pulmonary fibrosis (Heath *et al.*, 1968), permanently impaired lung function (Townshend, 1968), and disturbed liver function (Blejer and Caplan, 1971). Barrett and Card (1947) estimated that the lethal dose for a man doing light work would not exceed 2900 min mg/m^3. From these figures it may be estimated that a lethal exposure to Cd fume may result from breathing a concentration of approximately 5 mg/m^3 over an 8-hr period. In Blejer's fatal case, it was thought that the atmospheric concentration exceeded 1 mg/m^3. While completely preventable, fatal acute cases continue to occur (Lucas *et al.*, 1980).

Chronic Health Effects

A host of chronic effects attributed to Cd exposure have been reported by numerous investigators over the past three decades. Without doubt, at least in terms of human effects, the two cardinal pathologic lesions associated with Cd are pulmonary emphysema and renal tubular damage.

On the basis of data from studies of acute pulmonary effects, studies of long-term industrial exposure, and the general absence of contradicting animal data, it seems apparent that Cd-induced emphysema is related only to the inhalation route of exposure. Of more importance here is the discussion of health effects observed with chronic exposures via ingestion of Cd.

In addition to renal dysfunction, which has been clearly established as a major health effect of Cd, and which will be subsequently discussed, much concern has been expressed in recent years regarding the carcinogenic potential of Cd. Three main types of studies are involved in this issue: (1) studies investigating mutagenic properties utilizing both *in vivo* and *in vitro* test procedures; (2) studies of tumorigenic effects in experimental animals; and (3) epidemiologic studies of Cd-associated cancer occurrence in exposed humans.

Mutagenic Properties of Cadmium

A number of studies have examined the mutagenic potential of Cd in terms of chromosomal aberrations or mutations induced by *in vivo* exposure. Many of the more pertinent studies using this approach are summarized in Table 3. The dominant lethal test in mice has consistently yielded negative results, whereas occasionally other studies have reported chromosome changes as a result of Cd exposure. Human studies showing such effects, however, can be criticized on the basis of methodological deficiencies (EPA, 1979). In addition to chromosomal mutation studies using mammalian cell types, point mutation studies have investigated Cd effects in certain nonmammalian species, with mixed results as indicated in Table 4. At this point in time, there is no substantial evidence that human exposure to Cd results in heritable genetic damage, and the relationship between mutagenic activity in lower life forms and potential human carcinogenicity is conjectural. A wide variety of substances have now been reported to cause chromosomal aberrations in human leukocytes. The ultimate significance of such changes in terms of risk to human health is yet to be determined and should not be taken as credible evidence for Cd-induced carcinogenicity in man.

Tumorigenic Properties of Cadmium

This particular aspect of Cd toxicology has received a number of recent reviews (IARC, 1973, 1976; Carcinogen Assessment Group, 1977; NIOSH, 1976; Sunderman, 1977, 1978; Hernberg, 1977; and Nomiyama, 1980a).

Animal studies have amply shown that the injection of Cd metal or salts causes malignancies (sarcoma) at the site of injection and testicular (Leydig cell or interstitial cell) tumors distal to the injection site. These studies are summarized in Table 5. Injection site sarcomas arise from either subcutaneous or intramuscular administration. A large number of chemical irritants and physical agents are known to cause sarcomas in rodents, and "injection site" sarcomas are generally recognized as not being germane to human cancer, except perhaps by the direct injection route.

Leydig cell (interstitial cell) tumor formation has been obtained only after injections of high doses of Cd either directly into the testes or at sites distal to the testis. Histologically, these tumors are well differentiated, composed of Leydig cells, and retain their steroidogenic characteristics, although producing less testosterone than normal. The malignant potential of interstitial cell tumors is problematical. At present, probably the only entirely reliable criterion of malignancy is the presence of metastases (Roe *et al.*, 1964) and Cd-induced interstitial tumors have never been reported to metastasize. Also, such tumors can develop as the consequence of many other etiological factors, with the "spontaneous" development of intersitial cell tumors in rats varying considerably with the strain and age (Jacobs and Huseby, 1967; Malcolm, 1972). In addition, interstitial tumors of the testis are rare in man and account for less than 2% of all testicular tumors (Dixon and Moore, 1953). This tumor has yet to be reported in association with human exposure to Cd.

Several long-term feeding and inhalation studies with Cd have been carried out, but the induction of tumors has not been noted to occur as a result of more

TABLE 3
MUTATION STUDIES ON MAMMALIAN CELLS EXPOSED *in Vivo*

Author	Cells	Result and comment
Shiraishi and Yoshida (1972)	Human leukocytes from Itai-Itai patients	+ Increased chromatid breaks, isochromatid breaks, chromatid translocations, dicentrics, and acentric fragments.
Doyle *et al.* (1974)	Sheep leukocytes	+ Reported by EPA Carcinogen Assessment Group (1977).
Shimada *et al.* (1976)	Mouse oocytes	+ Reported by EPA Carcinogen Assessment Group (1977).
DeKnudt and Leonard (1976)	Human leukocytes from exposed workers	+ Chromatid aberrations and Leonard chromosome anomalies. Similar rate of effect in both high- and low-exposure groups. Chromatid breaks, exchanges.
Bauchinger *et al.* (1976)	Human leukocytes from exposed workers	+ Mixed-metal exposure (including Cd).
Bui *et al.* (1975)	Human leukocytes	– Swedish battery workers. – Itai-Itai patients.
Gilliavod and Leonard (1975)	Dominant lethal test in mice	–
	Mouse spermatocytes	– No translations.
	Mouse F_1 translocation test	–
Epstein *et al.* (1972)	Mouse dominant lethal test	–
Leonard *et al.* (1975)	Bovine leukocytes	– Heavy mixed-metal exposure (cadmium 50× control levels). Exposure fatal to 6 of 15 animals.
DeKnudt *et al.* (1973)	Human leukocytes	+ Mixed-metal exposure (including Cd).
Suter (1975)	Dominant lethal test in female mice	– Actual increase in living implants. No increase in dead implants.

TABLE 4
POINT MUTATION STUDIES WITH CADMIUM

Author	Organism	Result
Shabalina (1968)	*Drosophila*	–
Takahashi (1972)	*Saccharomyces*	+ Reported by EPA Carcinogen Assessment Group (1977)

relevant exposure routes and levels. Schroeder *et al.* (1965) have conducted lifetime exposure studies in Swiss mice where the animals were supplied with drinking water containing 5 ppm of Cd acetate. Although both males and females experienced some shortening of life span in comparison with the controls, the exposed animals had fewer tumors than the controls. Using rats at the same dosage, negative results were also obtained (Schroeder *et al.*, 1964).

Similarly, other oral exposure studies have yielded mainly negative results. For example, Levy *et al.* (1973) gave three groups of mice weekly doses (1.0, 2.0, and 4.0 mg/kg body wt) by gavage for 18 months. No difference between exposed and control animals was noted regarding general health or tumor incidence at 18 months. Similar experiments with hooded CB rats using doses of 0.2, 0.4, and 0.8 mg/kg of $CdSO_4$ weekly for 2 years were carried out by Levy and Clack (1975), with again no difference in tumor incidence in exposed and control groups. Decker *et al.* (1958) reported on another study using rats supplied $CdCl_2$ in drinking water in the following concentrations: 0.1, 0.5, 2.5, 5.0, 10.0, and 50 ppm as Cd. The highest dose group was terminated at 8 months because of appreciable stunting. There were no differences in body weight between control animals and those exposed to as much as 10 ppm Cd. Nor were there differences in food or water intake or any detected pathologic changes.

Anwar *et al.* (1961) exposed eight dogs to 0.5 to 10 ppm Cd (as $CdCl_2$) for 4 years. Aside from a benign splenic nodule in a dog treated with the lowest dose, no tumors were observed.

Paterson (1947) carried out inhalation studies with CdO and $CdCl_2$ fume using rats. No evidence of tumor formation was reported.

Malcolm (1972) gave rats up to 0.2 mg of $CdSO_4$ subcutaneously and up to 0.8 mg weekly by stomach tube for 2 years. In a third experiment, mice were given doses up to 0.02 mg/kg body wt subcutaneously at weekly intervals for 2 years. Except for a few sarcomas seen in the rats given subcutaneous injections and Leydig cell tumors (also seen in the controls), these studies were negative at the time reported. Several of the above briefly described oral intake and inhalation studies have been termed inadequate (IARC, 1976), apparently on the basis of the relatively small doses employed or the less than lifetime observation period employed.

Recently, Loser (1980) reported a 2-year Cd feeding study in rats. Doses of up to 50 ppm of $CdCl_2$ in food were employed. The 50-ppm level was considered to represent the toxic effect level under the conditions of the experiment. At this level some inhibition of weight gain was noted in males. Complete necropsies were performed on all animals. The mortality in all Cd-exposed groups was not

TABLE 5
ANIMAL TUMORIGENESIS INDUCED BY CADMIUM INJECTION

Author	Species	Compound	Route	Tumor and incidence
Haddow *et al.* (1961)	Rats	Cd-Containing ferritin	sc	Sarcomas (35%) Interstitial cell tumors
Heath (1962)	Rats	Cd powder	im	Sarcomas (75%)
Heath and Daniel (1964)	Rats	Cd powder	im	Sarcomas (90 and 75%)
Kazantzis (1963)	Rats	CdS	sc	Sarcomas (60%)
Kazantzis and Hanbury (1966)	Rats	CdS	sc	Sarcomas (60%)
Haddow *et al.* (1964)	Rats	$CdSO_4$	sc	Interstitial cell tumors (55%)
Gunn *et al.* (1963)	Mice	$CdCl_2$	sc	Interstitial cell tumors (77%)
	Rats	$CdCl_2$	sc	Interstitial cell tumors (68%)
Gunn *et al.* (1964)	Rats	$CdCl_2$	sc	Sarcomas (41%)
	Rats	$CdCl_2$	sc	Interstitial cell tumors (86%)
Gunn *et al.* (1967)	Rats	$CdCl_2$	sc	Sarcomas (10%)
Knorre (1970)	Rats	$CdCl_2$	sc	Sarcomas (13%)
Knorre (1971)	Rats	$CdCl_2$	sc	Interstitial cell tumors (40%)
Lucis *et al.* (1972)	Rats	$CdCl_2$	sc	Interstitial cell tumors (87%) Sarcomas (13%)
Reddy *et al.* (1973)	Rats	$CdCl_2$	sc	Interstitial cell tumors (80%)
Furst and Cassetta (1972)	Rats	Cd powder	im	Sarcomas (54%)
Favino *et al.* (1968)	Rats	$CdCl_2$	sc	Interstitial cell tumors (100%)
Malcolm (1972)	Rats	$CdCl_2$	sc	Sarcomas (?) Interstitial cell tumors (?)

increased over that observed in the control animals over the course of the study. No increase in total number of tumors or tumors for any specific site were found. No suggestion of dose-dependent increased tumor formation at any site was noted. Unfortunately, only one species was employed.

Obviously, some of the Cd doses used in past experiments were well below the maximum tolerable doses usually employed today in attempting to establish the carcinogenic potential of various substances. Nonetheless, there seems to be a rather large volume of negative animal data, which suggests that Cd is not tumorigenic at environmentally relevant exposure levels. In fact, Kerkvliet *et al.* (1979) have reported a dose-dependent inhibition of virus-induced tumor growth in those mice receiving Cd. Cadmium-exposed animals also demonstrated significantly higher levels of cell-mediated tumor cytotoxicity than controls.

Carcinogenesis in Man

Potts (1965) was the first to draw attention to the possibility of cancer in man as a result of Cd exposure. Previously, Friberg (1950) had noted three cases of cancer among seventeen deaths in alkaline battery workers. The sites were bladder, lung, and colon. While there was no control group, this would not seem an excessive number of cancer deaths, i.e., 17.6%. Potts reported on the causes of death of eight men with at least 10 years exposure. Five of the eight died of cancer. Their ages, years of exposure, and tumor sites are listed in Table 6. While recognizing that the number of cases were very limited, Potts felt that the association between cancer in man and Cd should be more "fully explored."

Kipling and Waterhouse (1967) surveyed a group of 248 workers exposed to CdO for a minimum period of 1 year. Twelve of these men had died and the causes of death were ascertained. The twelve include those reported by Potts. They computed the expected number of cases by site which would have occurred by chance and compared it against the observed. (Table 7).

From Table 7 it is obvious that there is a deficit of cancers at sites other than the four listed, i.e., only two were observed, but 7.53 would have been expected. It is unclear why the reported number of expected prostate cancer cases is so small, i.e., 0.58%, even adjusting for age. Cancer of the prostate is very common in elderly males and all three of Potts' cases were 65 or older. Although morbidity data are unavailable, cancer of the prostate in the United States is the third leading

TABLE 6
CANCER DATA[a]

Age	Years of exposure	Cause of death
75	14	Carcinoma of prostate
65	37	Carcinoma of prostate
53	35	Carcinoma of bronchus
65	38	Carcinoma of prostate
59	24	Carcinomatosis

[a] Adapted from Potts (1965).

TABLE 7
TUMOR MORBIDITY COMPUTATIONS[a]

Site of cancer	Number of cases		Probability of occurrence
	Expected	Observed	
All sites	13.13	12	0.660
Bronchus	4.40	5	0.449
Bladder	0.51	1	0.398
Prostate	0.58	4	0.003
Testis	0.11	0	0.898

[a] Reprinted with permission, from Kipling and Waterhouse (1967).

cause of cancer death in males aged 55–74, and the second leading cancer cause of death in males over 75. The percentages of cancer deaths due to prostate cancer for these two age groups are 7.6 and 19.3, respectively. Slightly over 2% of all U.S. male deaths and about 10% of cancer deaths are from this cause. The long-term incidence (death rate 13–14/100,000) trends for cancer at this site have not changed over the period 1940–1977. The death rates are similar for this site between England and Wales (11.51/100,000) and the United States (13.90/100,000) (NCI 3rd National Cancer Survey, 1977). It is of considerable interest that the mortality rates for cancer of the prostate in Japan, the country with by far the highest daily intake of Cd, are the lowest for any developed country in the world, i.e., 2.4/100,000 (Silverberg, 1980). This contrasts sharply with the rate for Sweden (21.9/100,000), which is the highest in the world. The Swedish daily intake and body burdens of Cd are among the lowest yet reported (Kjellström *et al.*, 1979).

Holden (1969), in a letter to the editor, mentioned two cancer deaths in Cd workers (prostate, bronchus). He gave no denominator data. It seems possible that these cases were included in the previous survey by Kipling and Waterhouse.

Lemen *et al.* (1976) conducted a retrospective cohort mortality study using reported causes of death among Cd smelter workers, who had at least 2 years of exposure in the years 1940–1968. Ninety-two deaths were known to have occurred out of the employee cohort of 292 white males. The observed number of deaths were compared with number of deaths expected (based on age and calendar time, and cause-specific mortality rates for the total U.S. white male population). There was a slight difference in total deaths between observed and expected (92 versus 99.32). This difference may be explained by the healthy worker effect. Only 24 deaths from heart disease were observed, and 43.52 were expected. The difference is significant at the $P < 0.01$ level. Twenty-seven deaths were observed as a result of malignant neoplasms, whereas 17.57 were expected. This is significant at the $P < 0.05$ level. Most of this excess was accounted for by neoplasia of the respiratory system where 12 were observed and 5.11 expected, a difference significant at $P < 0.05$. The risk of prostatic cancer was also elevated, i.e., 4 cases observed versus 1.15 expected, although this difference was not statistically significant. It should be pointed out that Lemen's group was exposed to arsenic, a well-documented human carcinogen, and Potts' group to Ni, another possible

human carcinogen. These elements may account for the increased incidence of respiratory tract tumors discussed in the above studies. Kjellström *et al.* (1979) have reported preliminary mortality data for 269 Cd–Ni battery workers and a control group of 328 alloy factory workers. Total cancer deaths were not statistically different in the two groups or from the general population. Prostatic cancer was not statistically increased in either group.

While of questionable relevance to the human prostate cancer question, Levy's (1973, 1975) specifically designed long-term rodent studies failed to detect evidence of prostatic neoplasia.

Humperdinck (1968) followed up eight cases of chronic Cd poisoning previously reported by Baader (1952). Four had died; one of lung cancer. Out of 536 workers with some Cd exposure he was able to find only five cases of cancer (including the one of lung cancer), and concluded his data did not support a causal relationship between Cd exposure and cancer.

McMichael *et al.* (1976) studied the mortality of workers from four rubber-producing plants. The standard mortality rate (SMR) was 94 for the full cohort. The SMRs for all cancer sites were not elevated, but at some specific sites an increase was noted: stomach, 148; rectum, 116; prostate, 119; all leukemia, 130; lymphatic leukemia, 158; and lymphosarcoma–Hodgkin's disease, 129. In addition to Cd, rubber plant workers are exposed to a great number of compounds, including the human carcinogen benzene, so the relationship of these tumors to Cd is highly problematical.

Kolonel (1976) suggested there may be an association between Cd and renal cancer. He determined the site-specific incidence of cancer for persons with an inferred occupational history of Cd exposure and for controls. Cadmium exposure was based solely on job classification information provided on admission to a cancer research hospital, making this procedure of dubious value in evaluating a causal relationship. The only significant association was with renal cancer. He had expected to find an increased incidence of prostatic cancer, but none was detected. To help substantiate and refine the association, he noted a fourfold increase in renal cancer among smokers with an occupation suggesting Cd exposure in comparison to controls. Tobacco, as previously mentioned, contains appreciable amounts of Cd. However, fewer nonsmoking Cd-exposed workers actually were found to have renal cancer than controls. This suggests that some other agent in tobacco smoke may be responsible, or that, at most, smoking is in some way synergistic with Cd. Obviously this is an extremely tenuous association. Among all the tumor sites specifically reported for Cd workers, many of whom probably were smokers, the kidney has yet to be mentioned.

In summary, there is no question that the injection of Cd into rodents results in injection-site sarcomas and interstitial cell tumors of the testis. Sarcoma production in rats is a common sequela to the injection of irritants and may be regarded as a nonspecific response to fibroblast injury. Interstitial tumors appear to result from the hyperplasia and metaplasia of tissue regeneration following vascular-mediated testicular damage. There is no evidence that these tumors are malignant neoplasms.

The human evidence for the carcinogenicity of Cd is insufficient to include it among the elements which are known to be human carcinogens. The reports on British battery workers and the work of Lemen *et al.* (1976) suggest an increase in prostate and lung cancer. These men were also exposed to Ni and/or As. Kolonel's (1976) work confirmed neither of these sites, but suggested an association with renal cancer. However, since Kolonel's data were based solely on job classification, his methodology was of dubious value. The geographic distribution of prostate cancer (Japan, Sweden, USA) suggests that an inverse relationship exists to Cd exposure. From the known mortality study data cited it might be argued that Cd exposure reduces general mortality, or is a potent protective factor against cardiovascular disease. In short, the presently available epidemiological evidence is inconclusive, based on small numbers, and usually confounded by exposure to other known carcinogens. The case for Cd as a carcinogen is not persuasive when the existing data are critically reviewed.

Renal Effects

There exists scientifically recognized agreement that renal tubular damage is the best-identified chronic health effect of Cd exposure (WHO Task Group, 1977; Criteria (Dose/Effect Relationships) for Cadmium, 1978). The earliest sign of this impaired renal function is assumed to be the appearance of low-molecular-weight (20,000–25,000) serum proteins, especially β_2-microglobulin, in the urine. With continued excessive Cd exposure, proteinuria is eventually followed by the onset of hyperexcretion of other substances, indicating the occurrence of increasingly severe Cd-induced renal impairment. Industrial studies have shown not only that proteinuria is much more common than emphysema, but also that it appears after shorter periods of exposure. β_2-Microglobulin is not the same protein as that excreted after conventional kidney damage and it does not react in the usual laboratory tests designed to detect urinary proteins (Browning, 1969). Its increased excretion has been used in known exposure situations to indicate the onset of Cd-induced renal dysfunction.

Friberg (1948) first reported proteinuria in workers exposed to CdO dust. β_2-Microglobulin has subsequently been reported in the urine of workers exposed to many forms of Cd, and in the urine of animals experimentally exposed. Cadmium accumulates in the proximal segment of tubular epithelial cells, which are located in the cortex of the kidney (Gunn and Gould, 1957; Axelsson and Piscator, 1966). Here it is bound to a low-molecular-weight cysteine-containing protein known as metallothionein. A high cysteine content enables the protein to bind as much as 5.8% cadmium (Kägi and Villee, 1960). As Cd accumulates in the cortex tubular reabsorption is inhibited, resulting in increased β_2-microglobulinuria and more general proteinuria (Berggard and Bearn, 1968).

Iwao *et al.* (1980) has postulated that β_2-microglobulin may have a threshold limit for reabsorption by the renal tubule. This group of workers has found a significant correlation between elevated blood cadmium and elevated β_2-microglobulin. This implies that increased urinary excretion of β_2-microglobulin is not necessarily indicative of cadmium-induced renal dysfunction. If subsequent investigation confirms this finding, the primary event from increased cadmium

absorption would appear to be the induction of increased β_2-microglobulin production by the liver.

The inhibition of tubular reabsorption may also result in glycosuria, generalized amino-aciduria, and phosphaturia, although proteinuria is the initial and most consistent abnormality. This mixture of findings is known as Fanconi's syndrome and is seen in Itai-Itai disease and in animals receiving repetitive injections of Cd. In rats these symptoms develop abruptly after the renal cortical concentration of Cd has increased approximately eightfold over control levels (Gonick *et al.*, 1975). The mechanism appears to be the inhibition of the ATP–Na–K–ATPase transport system (Gonick *et al.*, 1980).

In man, many diverse diseases, both acquired and inherited, are accompanied by Fanconi's syndrome, which, when severe, is recognized as a clinically significant medical problem. It represents a nonspecific pattern of proximal renal tubular absorption dysfunction and may vary widely in severity, spectrum of functional impairment, urinary findings, and ultimate prognosis. Table 8 lists a number of disease states and etiologic causes associated with Fanconi's syndrome, and amply attests to its multiple genesis.

Most experts agree that once clinically significant Cd-induced proteinuria is established it tends to persists throughout life (Piscator, 1966; Kazantzis, 1978).

TABLE 8
CAUSES OF FANCONI'S SYNDROME

I. Genetic
- A. Cystinosis
- B. Galactosemia
- C. Fructose intolerance
- D. Lowe's syndrome
- E. Medullary cystic disease
- F. Tyrosinemia
- G. Wilson's disease

II. Protein metabolism abnormalities
- A. Amyloidosis
- B. Myeloma
- C. Nephrotic syndrome (many causes)
- D. Sjogren's syndrome

III. Drugs and toxic agents
- A. 6-Mercaptopurine
- B. Isophthalanilide
- C. Degraded tetracycline
- D. Lysol
- E. Maleic acid
- F. Malonic acid

IV. Heavy metals
- A. Lead
- B. Mercury
- C. Uranium
- D. Cadmium

This constitutes a significant health effect for the affected individual. However, improvement and even cessation of proteinuria has been reported for some formerly occupationally exposed workers (Tsuchiya, 1976).

It is important to distinguish Cd-induced proteinuria from other more benign conditions, e.g., orthostatically induced β_2-microglobulinuria, or other genetic, toxic, or metabolic causes. Normal persons excrete an average of 0.1 mg/liter (Evrin and Wibell, 1972) with a day-to-day variation of 50 to 100%. Exercise is known to result in temporarily increased excretion. However, the daily excretion level for Cd-exposed workers with proteinuria is often 100 to 1000 times that of normal levels (Shiroishi *et al.*, 1977). It now seems firmly established that radioimmunoassay is the most sensitive indicator of β_2-microglobulinuria (Shiroishi *et al.*, 1977) and electrophoretic methods probably underestimated its incidence.

Similar high levels of β_2-microglobulin and other proteins have also been found in healthy farming women where increased excretion was strongly correlated to residence time in exposed areas and the use of Cd-contaminated river water (Kjellström *et al.*, 1977b). Tsuchiya *et al.* (1979) have found that β_2-microglobulin excretion is highly correlated with aging in both high- and low-Cd-exposure population groups.

While there is general agreement that the impact of Cd is upon the renal tubule, evidence is now beginning to accumulate indicating there is also some effect upon the renal glomerulus, resulting in the excretion of higher-molecular-weight proteins (Bernard *et al.*, 1978, 1979; Roels *et al.*, 1978a; and Lerner *et al.*, 1979). None the less, elevated β_2-microglobulin excretion appears to be the earlier event.

The ultimate prognosis of Cd-induced renal abnormalities is the principal basis in assessing the impact of this element on human health. While pointing out that the relationship of Cd proteinuria to life expectancy is unknown, Kazantzis (1977) believes it is evidence of a "critical" effect. Adams *et al.* (1969) long-term observations, however, indicate that some men have had proteinuria for many years without serious impairment of their health status. He notes that retired men do not seem to have more serious renal disease than those still at work, and there is no good evidence of progression to terminal renal failure. It would seem reasonable to conclude that, in the vast majority of cases, a moderate increase in excretion of β_2-microglobulin may be a relatively mild, nonprogressive condition. On the other hand, as seen in certain occupational cases with prolonged exposure, β_2-microglobulin excretion is associated with the later appearance of more severe symptoms in some individuals (Kazantzis, 1978). While it is true that Cd exposure causes an increase of β_2-microglobulin excretion and represents a sensitive indicator of exposure, Nomiyama (1980a) has criticized the characterization of β_2-microglobulinuria as renal dysfunction by pointing out that it may increase with age and be independent of renal dysfunction. However, given the potential for proteinuria to be associated with more serious renal dysfunction, prudent public health measures are in order to assure that Cd exposure levels do not result in kidney accumulations sufficient to produce proteinuria.

An examination of available vital statistics and other demographic data from Japan is also of some value in attempting to assess ultimate prognosis (Kato and

Abe, 1978). The area of Japan having the highest level of environmental Cd exposure is located along the Jinzu River in Toyama Prefecture, where mining operations originally began 370 years ago. This is the area where Itai-Itai cases were formerly endemic, consisting of Fuchu Town and numerous small hamlets. Daily dietary Cd levels for the area average 140 μg per day for women (range 20–370) and 180 μg per day (range 50–470) for men. The incidence of proteinuria in the area increases with age and exceeds 20% for some older age groups. Statistics for Toyama Prefecture indicate that the death rates are higher than for Japan as a whole for nearly every disease category, including nephrosis and nephritis. In Fuchu, the death rate for nephritis and nephrosis is approximately 32/100,000 compared to about 20/100,000 for Japan as a whole. This increment, even if entirely due to Cd, which seems unlikely in view of the similar trend seen for other diseases and total mortality, translates to less than three excess renal deaths per year for Fuchu. This would seem to liberally represent the worst-case situation and suggests that Cd-induced proteinuria relatively infrequently leads to endstage renal disease. Kjellström *et al.* (1979) have recently reported mortality data for a group of Swedish Ni–Cd battery workers who died between 1949 and 1975 having at least 5 years Cd exposure. While designed to study cancer mortality, 5 of the 43 deaths were attributed to kidney failure. While the numbers are too small for statistical analysis, he concluded that for workers who began before 1948, there was increased general mortality due largely to respiratory disease, but that renal disease mortality was also increased for this group. Before 1947 the Cd exposure levels averaged more than 1000 $\mu g/m^3$ in this plant.

On occasion the renal lesion appears to be severe enough to eventually produce osteomalacia and multiple fractures, as in Itai-Itai disease. However, in all such cases (Friberg *et al.*, 1974; Nicaud *et al.*, 1942; Adams *et al.*, 1969) there appears to be multiple dietary deficiencies (Ca, protein, Vitamin C, Vitamin D) in addition to an excessive Cd exposure. For example, Itai-Itai disease occurs almost exclusively in grand multiparous women over the age of 50 who live predominantly on a rice diet containing a high Cd content. The Japanese Government has monitored new cases of Itai-Itai disease since 1969 (Shigematsu *et al.*, 1979). Nicaud's cases occurred under wartime factory conditions in France. It seems apparent that multiple nutritional deficiencies have to be present for Cd to produce this complex disorder. Nomiyama (1980b) has reviewed reported cases of occupational Cd-induced osteopathy, the majority of which were reported from France during or immediately after World War II. Most responded to small amounts of Ca and Vitamin D. No cases have been reported from Sweden, Japan, or the United States. While the bone changes (osteomalacia) have been assumed to be secondary to the renal defect, it has been shown in animals that Cd may directly cause osteoporotic bone changes (Yoshiki *et al.*, 1975; Takashima *et al.*, 1980). Other authors have been unable to induce osteomalacia in a variety of experimental animals (mice, rabbits, and monkeys) despite the ready induction of renal tubular dysfunction (Nomiyama *et al.*, 1980). Such evidence implies that certain segments of the population living on subsistence diets or diets deficient in Ca, Fe, and/or Zn may well be at increased risk from Cd.

In summary, the data discussed above argue strongly in favor of renal tubular

dysfunction (as indexed by proteinuria and certain other signs) being considered as the critical effect associated with chronic Cd exposure via ingestion. Also, certain data indicate that the critical effect of renal tubular dysfunction, once induced by Cd exposure, is often irreversible and constitutes a clear-cut significant adverse health effect.

DOSE–EFFECT/DOSE–RESPONSE RELATIONSHIPS

The kidney (kidney cortex), as indicated above, is generally accepted as being the critical organ for the chronic exposure effect of Cd. It is the first organ demonstrating functional changes in response to excessive exposure to Cd. The mean Cd concentration in the critical organ (renal cortex) when the critical effect (proteinuria) appears is the critical concentration (Subcommittee on the Toxicology of Metals, 1976). Therefore, it is appropriate to discuss data that define relationships between Cd exposure and effects on renal function. In particular, increased β_2-microglobulin excretion is typically taken as the main biochemical index of the earliest manifestation of the critical effects of Cd-induced renal dysfunction (i.e., proteinuria). β_2-Microglobulin has therefore been used as a readily accessible biochemical marker, signalling the onset of renal tubular dysfunction which, with continued excessive exposure, may lead to severe renal impairment (e.g., glycosuria, phosphaturia, etc.).

Dose–Effect Relationships

Regarding the definition of critical concentration(s) of Cd in the kidney necessary for the induction of renal dysfunction, a range of estimates has been reported by different investigators. For example, as presented in Table 9, animal studies on a number of different species have generated data suggesting that renal dysfunction may be initiated at kidney cortex concentrations ranging from 56 to 700 μg/g wet wt. The bulk of the studies, however, have generated estimates for a variety of mammalian species that range from approximately 150 to 450 μg/g, with findings for nonhuman primates tending toward the upper end of the range (i.e., over 300 μg/g). Studies by Ellis *et al.* (1981), using *in vivo* measurements of kidney Cd levels, suggest that the critical concentration of Cd in the kidney cortex for man is 300–400 μg/g. Using a similar methodology, Roels *et al.* (1979) suggested a figure between 200–250 μg/g and point out that at least 95% of the USA and European middle-age population are at least a factor of 5 below this critical level.

On the basis of certain animal data of the above type and limited human autopsy data (28 cases), Friberg *et al.* (1974) proposed that 200 μg/g wet wt of kidney cortex be considered as the critical concentration for Cd-induced renal proteinuria. The WHO Task Group (1977) and the Subcommittee on the Toxicology of Metals (1976) under the Permanent Commission and International Association of Occupational Health have tentatively endorsed this proposal for Cd. Not all investigators agree, however, that 200 μg/g is the best estimate of the critical renal cortex concentration. Brown *et al.* (1978) discussed the need to study disease patterns in persons with various concentrations of Cd in the renal cortex to establish the critical renal concentration. In the absence of such data, they suggest a value

TABLE 9
CRITICAL CONCENTRATION OF CADMIUM IN ANIMALS[a]

Animal species	Abnormality	Cadmium level in renal cortex (μg/g)	Investigator	Year
Mouse	Proteinuria	170–250	Nordberg *et al.*	1972
		150	Nomiyama *et al.*	1977
	Glycosuria	150	Nomiyama *et al.*	1977
Rat	Proteinuria	150	Suzuki	1974
		156	Murakami *et al.*	1974
	Low-molecular-weight proteinuria	90	Piscator *et al.*	1972
		200	Kishino *et al.*	1975
	Pathological changes	400	Bonnell *et al.*	1960
		56	Kawai *et al.*	1976
Rabbit	Proteinuria	300–700	Friberg	1950
		142	Katagiri *et al.*	1973
		300	Nomiyama *et al.*	1974
		230	Nomiyama *et al.*	1976
	Glycosuria	117	Katagiri *et al.*	1973
		300	Nomiyama *et al.*	1974
	Aminoaciduria	200	Nomiyama *et al.*	1974
		230	Nomiyama *et al.*	1976
	Enzymuria	117	Katagiri *et al.*	1973
		200	Nomiyama *et al.*	1974
	Decreased tubular function	250	Piscator *et al.*	1970
		238	Nomiyama *et al.*	1973
	Pathological changes	250	Axelsson *et al.*	1966
		250	Stowe *et al.*	1972
Monkey	Proteinuria	450	Nomiyama *et al.*	1978
	Low-molecular-weight proteinuria	380	Nomiyama *et al.*	1978
	Glycosuria	450	Nomiyama *et al.*	1978
	Aminoaciduria	450	Nomiyama *et al.*	1978
	Pathological changes	300–465	Nomiyama *et al.*	1978

[a] Reprinted, with permission, from Nomiyama (1980a).

of 50 μg/g wet wt as the estimate of critical concentration, since there is no evidence that levels of 50–200 μg/g do not produce some adverse health effect.

Nomiyama (1977) noted that estimates of the critical concentration from human data might be more appropriately derived from cases where proteinuria was the only pathological finding, so that renal Cd concentration measurements were less likely to have been affected by possible reductions in renal Cd levels from those present at the onset of renal dysfunction. Such reductions in renal concentrations are thought to occur due to increased outflow of Cd that commences sometime after the onset of renal tubular damage. Nomiyama (1977) noted that, from among the eight human autopsy cases of the WHO Task Group (1977) reported to have proteinuria only, renal cortex Cd concentrations ranged from 21 to 395 μg/g wet wt, with all but one being at least 150 μg/g and four exceeding 300 μg/g. On this

basis and other supporting data derived from his studies on monkeys, Nomiyama (1977) suggested that 300 μg/g may be a more accurate estimate than 200 μg/g for the critical concentration of Cd in renal cortical tissue.

Regardless of whether 200 or 300 μg/g is taken as being the better estimate of a theoretical critical concentration, it should be remembered that, in either case, a "threshold" Cd concentration necessary to induce renal dysfunction is implied. This may not fully reflect that significant individual variation in susceptibility demonstrated by both human and animal studies.

Nonetheless, at the present time, 200 μg/g is the most widely accepted estimate of the critical concentration for the induction of renal tubular dysfunction (Friberg *et al.*, 1974; Subcommittee on the Toxicology of Metals, 1976; Criteria (Dose/Effect Relationships) for Cadmium, 1978).

It is of interest to compare the current levels of Cd in the renal cortex of the American population to the critical concentration. Age is important, since Cd tends to increase in the kidney from birth to approximately age 50 and then decreases. Kidney tissue is obtained at autopsy of accident victims for such determinations. Results for apparently normal adults from several studies are presented in Table 10.

All data collected in the United States on Cd in kidney cortex tissue indicate that the mean level reached is generally in the range of 20 to 35 μg/g wet weight. Only about 0.6% of the results exceed 100 μg/g and none has been close to the 200 μg/g level. In the studies which separated smokers, the smokers had 70 to 100% higher values than nonsmokers.

Dose–Response Relationships

Defining the relationship between dose (or exposure) and response on a quantitative basis becomes difficult, because the effect is the result of an accumulation of Cd over time rather than a one-time dose. Further complicating the picture, the variability of absorption rate(s), retention, effect level, and dose have to be considered on an individual basis and integrated into a population base. There have been two major types of approaches utilized to attain these goals.

In the first type, various authors have attempted, by means of metabolic models, to estimate the total Cd exposure necessary to cause a designated critical Cd

TABLE 10
CADMIUM IN THE KIDNEY CORTEX OF U.S. ADULT POPULATION (μg/g)

Reference	Age	*N*	Mean	Standard deviation	Range
Tipton and Cook (1963)	Adults	145	35	16	6–88
Indraprasit *et al.* (1974)	31–80	134	22	14	—[a]
Gross *et al.* (1976)	39–85	28	30	—	7–101
Johnson *et al.* (1977)	40–59	59	26	8	4–109
Hammer *et al.* (1973)	40–79	58	29	—	6–83
Morgan (1972)	62 mean	100	33	—	1–128

[a] Data not presented.

accumulation in the renal cortex. Obviously, the Cd dose necessary to produce the defined critical concentration will be influenced by the assumptions used in the model. For instance, the rate of absorption used will greatly affect such calculations.

Some of the results obtained, with the use of metabolic models as reported by Friberg *et al.* (1974), are summarized in Table 11. Two types of calculations are presented in the table: those pertaining to the absorbed doses necessary to achieve a kidney cortex concentration of 200 μg/g, and those pertaining to corresponding exposures necessary to achieve that concentration. All calculations are made for two estimates of biologic half-time for Cd: 19 and 38 years. For a 50-year exposure, a daily retention of 10 μg/day would be sufficient, assuming the 38-year estimate of biological half-time, to achieve the 200 μg/g level in the kidney cortex. Although an effect of estimated biological half-time on retained Cd necessary to reach the critical concentration in the kidney cortex is readily apparent, this effect is small in comparison to that of exposure duration.

The remainder of the table demonstrates the effect of biological half-time on the daily exposures necessary to achieve the critical concentration in the cortex. Given the assumptions listed in the table, a daily dietary intake of 248 to 352 μg of Cd would be sufficient over a 50-year exposure period for the critical concentration to be reached.

Kjellström and Nordberg (1978) developed a more elaborate model in order to overcome some of the uncertainties associated with the earlier version. Using this model, they conclude that the renal cortex concentration of nonsmokers would reach 200 μg/g wet wt at an average daily Cd intake via food of 440 μg/g wet wt for a European–American population and 325 μg for a Japanese population. The latter group is lower because of smaller body size and kidney weight.

TABLE 11

CADMIUM EXPOSURE REQUIRED FOR REACHING A KIDNEY CORTEX CONCENTRATION OF 200 μg Cd/g USING DIFFERENT ALTERNATIVES FOR BIOLOGICAL HALF-TIME IN KIDNEY CORTEX AND EXPOSURE TIME[a]

Basis of calculation	Exposure time (years)	Levels of cadmium intake or retention yielding renal dysfunction, assuming cadmium half-time of:	
		38 years	19 years
		Daily retention (μg)	
Constant daily retention during whole exposure time	10	36	39
	25	16	20
	50	10	14
		Daily cadmium intake (μg)	
Food exposure for 50-year-old person (2500 cal/day, 4.5% retention; changing caloric intake by age accounted for)	50	248	352

[a] Compiled from data by Friberg *et al.* (1974).

Another group evaluating dose–response relationships for Cd has estimated the ingestion intake level producing the critical concentration of Cd to be around 200 μg daily, corresponding to an actual absorption of 12 μg/day (Criteria (Dose/Effect Relationships) for Cadmium, 1978). For smokers this estimate is reduced by about 1.9 to 10.1 μg, which corresponds to an oral intake of 169 μg. Using a second approach based on metabolic modeling of the above type, this same group derived an ingestion level to produce the critical concentration of 248 μg daily when pulmonary absorption is negligible.

As can be seen from the preceding discussion, varying estimates of total daily dietary intake yielding the critical renal cortex concentration have been generated. Based on the above types of calculations, it seems that a daily Cd intake of 200 μg from all sources would represent a reasonable estimate of lifetime ingestion which would result in the critical concentration being reached in nonsmokers.

For smokers the dietary intake level sufficient to eventually reach the critical renal cortex concentration of 200 μg/g is lower, being reduced by approximately 25 μg per pack of cigarettes smoked each day. Thus, for individuals smoking 1, 2, or 3 packs per day, dietary levels of 175, 150, and 125 μg/day, respectively, can be projected as yielding the critical concentration. These calculations are quite simplistic and conservative, since heavy smoking is not likely prior to the second decade of life.

Several epidemiological studies in Japan provide empirical support for the existence of Cd-induced renal tubular dysfunction. Nogawa (1978) and Nogawa and Ishizaki (1979) described the results of dose–response data obtained on inhabitants of the Jinzu River Basin in the course of a 1967 epidemiological study, which has been previously published in detail (Fukushima *et al.*, 1974). Proteinuria with glycosuria was used as an index of renal tubular dysfunction, and the prevalence of proteinuria and glycosuria among Jinzu River Basin inhabitants was determined in relation to the average levels of Cd found in the rice of their respective villages in 1972. A close dose–response relationship between Cd exposure and health effects was found to exist when the inhabitants were arranged according to their village average rice Cd concentrations and residence time in the polluted area. Significant differences in proteinuria prevalence, compared with the control, were observed at the levels of 0.30–0.49 μg Cd/g in rice and greater. It was also found that Cd concentration in urine, when normalized for creatinine, was related to indices of health effects for inhabitants of the Jinzu River Basin (Nogawa *et al.*, 1979).

Nogawa also described the outcome of a similar dose–response analysis that he carried out on the results of an epidemiological study (Muramatsu, 1974) of Itai-Itai disease conducted by Ishikawa Prefecture Health authorities in 1974 and 1975 in yet another area of Japan, the Kakehasi River Basin (Nogawa, 1978; Nogawa *et al.*, 1978). In that study, retinol-binding protein excretion was employed as a measure of the proteinuria that typifies the symptomatology associated with renal tubular dysfunction. The prevalence of proteinuria among the Kakehasi River Basin inhabitants was plotted, by age, against the average rice Cd concentrations found in their respective villages. A dose–response relationship was again found

between average village rice Cd concentrations and proteinuria prevalence when the rice exceeded 0.50 μg Cd/g.

From these studies Nogawa and Ishizaki (1979) estimated the maximum allowable average daily intake level should be under 201-287 μg to prevent renal tubular damage. Evidence was also presented that pollution in the Jinzu River Basin was probably maximal between 1910 and 1950 and has declined since that time. This may explain the preponderance of abnormal urinary findings only in persons over age 50. The use of current levels of Cd in rice in these calculations results in conservative intake values.

These Japanese results are about the same as the estimated 250 μg/day given by Friberg *et al.* (1974) as the level resulting in the critical kidney concentration being reached. The Cd ingestion level for a Western European or American population with correspondingly larger body size would be expected to be proportionally greater.

A second approach utilized for obtaining dose–response relationships has attempted to expand the calculations from individual exposure to populations and average exposure.

Kjellström (1977, 1978) reported a detailed assessment of dose–response in humans involving both calculated and epidemiological data, using tubular dysfunction indexed by β_2-microglobulin excretion as the percentage of a European/American population that would have kidney cortex Cd concentration exceeding 200 μg/g. One difference of this model from the calculations of others is that it considers variations within the population which result in some percentage being at risk from very low levels of exposure.

In analyzing the model and its predicted results, several of its aspects, including certain key assumptions, should be examined. For instance, in applying the model, Kjellström *et al.* (1977a) defined excessive β_2-microglobulin excretion as that exceeding 290 μg/liter, i.e., the 95% confidence level based on a geometric average excretion of 84 μg/liter for normal unexposed persons. Kjellström *et al.* (1977a) are careful to point out that elevated chronic excretion of β_2-microglobulin does not equate with clinically significant proteinuria and that its definition was designed for comparative epidemiologic purposes.

In his thesis, Kjellström cites observed response rates for control populations of 3.4% for Sweden, and 2.5 to 3.2% for Japan (Kjellström, 1977). With such prevalence rates, which undoubtedly involve many other factors which were discussed previously, the significance of percentages less than 4 to 5% attributed to Cd is questionable.

The Kjellström model uses mean intake values to calculate mean kidney cortex values (Kjellström and Nordberg, 1978), and vice versa. Based on Kjellström's finding (Kjellström, 1977) that the geometric standard deviations of Cd in kidney cortex and daily intake from a different population were approximately the same at relatively low Cd intakes, he assumed this same relationship existed for other Cd intakes. He found the kidney cortex geometric standard deviation varied between 1.6 and 2.5. However, this apparently small range makes a large difference in the tails of the distribution curve. Based on the distribution of kidney cortex

data (Elinder *et al.*, 1976) from persons with relatively low Cd concentrations, he applied the same geometric standard deviation of 2.35 to the relatively high average Cd intake of 440 μg/day. The calculated percentage of a European/American population that would have kidney cortex Cd concentrations exceeding 200 μg/g for a given daily Cd intake over a 50-year period is expected to approximate the following distribution (Kjellström, 1978): 0.1%—32 μg Cd/day; 1.0%—60 μg Cd/day; 10%—148 μg Cd/day; and 50%—440 μg Cd/day. The validity of including the low values is debatable.

Kjellström (1977) presents data from three groups of Japanese in an equivalent dose–response framework. There is agreement between his metabolic model-derived dose–response lines and the observed Japanese data over the range of 40 to 400 μg Cd/day. The response rates predicted by the Kjellström model, therefore, appear to have some empirical support and should not be disregarded in risk assessment evaluations for Cd.

Population at Risk

A number of populations at likely special risk for adverse effects of Cd exposure were implied or identified in the course of the above discussions. For example, smokers were noted to have about 2 to 3 times the prevalence of proteinuria found for nonsmokers (Kjellström *et al.*, 1977a). This and other evidence cited earlier identify smokers as being a group at special risk. Actually, they are probably the group at greatest risk.

It is also recognized that approximately 100,000 Americans have potential occupational exposure to Cd (NIOSH, 1976). The spectrum of occupational exposure varies from negligible to those situations producing acute and/or chronic toxicity and even death.

In an analogous manner, persons with severe nutritional deficiency, e.g., Fe, Ca, Zn, protein, Vitamin D, etc., which may be aggravated by Cd are conceivably at special risk. Human data concerning these effects are scant. Such a risk is hardly surprising and is obviously additive since these deficiencies can, in and of themselves, be sufficient to cause disability and/or fatal disease.

Persons with diets which include more than normal amounts of leafy vegetables, visceral meats, fish, and shellfish may also be at increased risk, because these food groups can contain rather large amounts of Cd. Animal studies (Engström and Nordberg, 1979; Kello and Kostial, 1977; Kostial *et al.*, 1978) indicate that age is a significant factor in Cd metabolism, due to the marked increase in intestinal absorption in young animals. Lactating women may also have increased absorption due to their negative Ca balance. Any incremental Cd absorption in children or lactating women is unlikely to substantially alter total body burden viewed from the lifetime perspective and the current Cd levels in the American diet. Regarding all these populations at risk, one cannot now describe the precise effects of additional incremental exposures to Cd. One can only assume their greater susceptibility to potential health effects from Cd than the average population.

Maximum Allowable Exposure

From the foregoing it can be concluded that total exposure equivalent to 200 to 350 μg/day of ingested Cd is the generally accepted level projected to result in the

critical renal concentration of 200 μg/g wet wt of cortex over a 45- to 50-year period. Among the most susceptible members of the population, this exposure could cause renal dysfunction.

CURRENT RISK EVALUATION

It has generally been concluded that ingestion of 200 to 350 μg Cd/day over a 50-year exposure period is a reasonable estimate for individuals (excluding smokers and occupationally exposed) within the population to reach the critical renal concentration (200 μg Cd/g wet wt in the renal cortex) associated with the initiation of proteinuria. This ingestion limit assumes background exposure levels of air and no exposure from smoking. If these exposures are increased, then the suggested ingestion limit must be correspondingly reduced. Smoking one pack of cigarettes/day will reduce the limit by about 25 μg/day. Again these exposures are assumed to occur over a 50-year exposure period and, in the case of cigarettes, since many smokers start as teenagers, this addition would be relevant for much (30 to 35 years) of the 50-year exposure period. Therefore, smokers must be considered as being at increased risk.

A number of factors must be assumed to delineate the risk of allowing increased Cd content of agricultural soils. These include diet preference, crops to be grown, degree of dilution of the crops by marketing, and management practiced during crop production.

Diet

Two types of dietary information are available: The FDA Compliance Program (Compliance Program Evaluation, 1974) and a diet for lacto-ovo-vegetarians. The FDA diet is that of an average teenage male, and therefore overestimates the lifetime consumption rate for these foods. For lacto-ovo-vegetarians, the average daily intake provided by Loma Linda University (1978) was used (Table 12). According to this source, pure vegetarians (i.e., those consuming no dairy products or eggs) are quite rare even among Seventh Day Adventists. It is interesting to note the Loma Linda data indicates the lacto-ovo-vegetarian diet is no higher in Cd than the normal diet, contrary to what is sometimes assumed. However, the Cd intake might be higher for the vegetarian who consumes additional grain and vegetable products in place of dairy products. This vegetarian diet, however, must be more critically examined. It must be remembered that these values represent average diets and do not reflect the distribution of diets that can occur. If individuals with a normal diet substitute potatoes for legume vegetables and fruits, they can increase their Cd intake by 12.7 μg/day without changing the total calories they consume. If they substitute fruits for potatoes, however, they can reduce their Cd intake by 8 μg/day. It would also seem logical to assume that individual preferences for certain foods within a food class will alter the amount of Cd consumed by an individual. Since the FDA diet is for the large food consumer, and no better working base is known, these diets (FDA Compliance Program Evaluation and Loma Linda lacto-ovo-vegetarian) will be used to represent current exposure and for purposes of determining potential increase in Cd exposure.

TABLE 12
FOOD CONSUMPTION AND CADMIUM INTAKE

Food classes	ppb Cd[a]	Vegetarian diet[b]		Normal diet[c]	
		g/day	μg Cd/day	g/day	μg Cd/day
Dairy products	5.7	584	3.3	549	3.1
Meat, fish, poultry	15.3	—	—	204	3.1
Grain and cereal products	23.2	203	4.7	331	7.7
Potatoes	48.0	43	2.1	138	6.6
Leafy vegetables	40.5	252	10.2	42	1.7
Legume vegetables	6.2	166	1.0	51	0.3
Root vegetables	32.3			25	0.8
Garden fruits	14.7			69	1.0
Fruits	3.0	284	0.8	173	0.5
Oily fats, shortenings	15.3	107	1.6	56	0.9
Sugars and adjuncts	10.0	110	1.1	65	0.7
Beverages	3.0	600	1.8	534	1.6
Total		2349	26.6	2237	28.0

[a] From FDA Compliance Program Evaluation (1974) Total Diet Studies.

[b] Loma Linda lacto-ovo-vegetarian diet. Based on response of 183 southern Californians in a food frequency questionnaire by the Department of Biostatistics and Epidemiology, Loma Linda University School of Health, 1978. Leafy vegetable class includes garden fruit and root vegetable classes from normal diet.

[c] Adjusted on a caloric basis from the FDA 1974 Total Diet Studies to represent the normal diet which compares with the adult lacto-ovo-vegetarian diet.

Soil–Plant Response

The Cd content of food is influenced not only by the type of food consumed but by the plant variety, and soil conditions under which it is produced. For brevity, only a synopsis of the literature on soil–plant response is included here. For a more complete review see Page *et al.* (1980) and Nriagu (1980).

In natural soils, the Cd content varies with the nature of the parent rock, being high in soils on basaltic rock and low in soils on granitic rock (Baes, 1973). Unpolluted soils have a range of 0.01–22 μg Cd/g (Allaway, 1968; Lund and Page, 1980) with 0.06–0.5 μg Cd/g being considered normal. Unpolluted soils of greater than 1 μg Cd/g are found in unusual geochemical enrichment areas. Soils changed by human activity (atmospheric fallout, waste addition, and/or phosphorus fertilizer additions) can have considerably higher concentrations of Cd (Williams and David, 1976; Ryan, 1976; Fleischer *et al.*, 1974).

The mobility and persistence of Cd in soils depends on the physical and chemical characteristics of the soil as well as the chemical form of Cd. Small, but significant, increases in Cd concentration of leachate with increased sewage sludge application in a given year have been reported (Hinesly and Jones, 1976), but the mean Cd concentration in drainage water did not appear to increase with increased years of sludge application. Leaching of Cd from disposal sites containing Cd-plating waste and mine tailings under acidic conditions have been

documented (Perlmutter and Lieber, 1970; Mink *et al.*, 1972) and the latter accounts for the two reported instances of adverse health effects in the general population, i.e., in Japan (Friberg *et al.*, 1974) and England (Carruthers and Smith, 1979). However, the English report is still regarded as conjectural (Kraemer *et al.*, 1979; Hughes and Stewart, 1979). In general, it is the opinion of the agricultural community (CAST Report, 1976) that under normal conditions in agriculture systems, the vast majority of applied Cd stays in the zone of incorporation. This leads to the conclusion that soil is an ultimate receptor of environmentally released Cd. If so, then the observation of Hunt *et al.* (1971) on the atmospheric contamination and dust fallout of Cd results in the hypothesis that soils will continue to increase in Cd concentration as long as Cd is released to the environment.

The general assumption that plant uptake of Cd is related to its level in the soil solution has recently intensified the desire to understand Cd chemistry in soils. The lack of definitive information on Cd chemistry in soils and the chemical similarity of Cd and Zn (Allaway, 1968; Fulkerson and Goeller, 1973) have led to the assumption that, in general, the reactions of Zn and various metals in soil may be useful indicators of the behavior of Cd in soils.

Numerous reviews of metal reactions in soil are available (Hodgson, 1963; Jenne, 1968; Ellis and Knezek, 1972; Lindsay, 1973; Stevenson and Ardakani, 1972). From these reviews it is apparent that many soil components (clay, organic matter, hydrous metal oxides, carbonates, and inorganic compounds) have the ability to sorb metals in soil, and thus to reduce the concentration of soluble metal. The soil pH has a pronounced effect (negative correlation) on the solubility of Cd. However, even this effect can be a function of the solid phase present. For example, Andersson and Nilsson (1974) examined Cd sorption by several soil materials as a function of soil pH. They found that in the presence of iron oxides there was no sorption of Cd below a pH of 4.5, but at pH 6 most of the Cd was sorbed. However, organic matter sorbed most of the Cd even at a pH of 4.0. It was also demonstrated that the type of clay fraction had a significant effect on the distribution of Cd.

The work of Santillan-Medrano and Jurinak (1975), Fassbender and Seekamp (1976), and Street *et al.* (1977) demonstrated that measured soluble Cd was less than that predicted by the least-soluble inorganic Cd compounds. Street *et al.* (1977) demonstrated that soluble Cd was usually greater than Cd activity, and the discrepancy increased as organic matter content of the soil increased, suggesting that organic complexation was responsible.

In the last decade, information about Cd in soils and plants has grown at a rapid pace. A few soil factors have been found to have a consistent effect on Cd accumulation in nearly every crop. These include soil pH and organic matter. Other soil constituents/characteristics have been proposed from theoretical considerations and observations, but have been found not to be as consistently important: CEC; clay content or type; Zn; Fe, Mn, or Al oxides; PO_4; K; Ca; Cu; and Ni. These latter factors may be important, but the lack of definitive data will not allow that conclusion to be drawn at this time.

Studies of the effect of soil pH on Cd accumulation by different plants have

nearly always found accumulation in neutral soils to be lower than that in moderately-to-strongly acidic soil. Chaney *et al.* (1975) found that soybean leaf Cd declined in a smooth continuous curve as soil pH rose from 5.3 to 7.1, indicating no sharp change in soil-sorbing capability as pH increased.

In field studies with sludge-applied Cd, plant uptake of Cd is generally reduced by liming, but the extent depends on crop and perhaps soil. Several studies which included unlimed and limed plots for each sludge rate found strongly decreased Cd (80–98%) for limed plots in leafy and root vegetable crops, but less decrease (0–70%) in soybeans or oats (Chaney *et al.*, 1977; Chaney and Hornick, 1978).

Plant uptake (concentration) of Cd is a function of many variables, but it has generally been found that for a system (constant soil, pH, plant, etc.) the plant concentration of Cd generally exhibits a highly signficant positive linear correlation with Cd added to the soil. The slope of this relationship can be altered by several variables (soil, plant, pH, etc.), but it remains linear. This has led to an assumption that limiting the amount of Cd added to the system will limit the concentration of Cd in plants. The concept of soil Cd vs plant Cd is supported by the long-term land application sites studied by Ryan (1976), Chaney and Hornick (1978), and Otte and LaConde (1977). From these studies it is evident that the variables of pH, soil, and crop influence the slope of the response curve. There is also a significant relationship between soil and plant Cd, even when none has been applied for a number of years. This same kind of information can be gleaned from the work of Williams and David (1973, 1976) and Mulla *et al.* (1980) on long-term superphosphate plots. The implication is, once the Cd is added to the soil, a fraction of its remains in a plant-available form for an extended period of time.

The CAST Reports (1976, 1980) indicate that there are unequal plant effects from equal Cd applications, depending on the mode of application: for example, single application vs repeated applications where the cumulative amount of Cd applied is equal. This concept is supported by the work of Hinesly *et al.* (1976, 1979), Dowdy *et al.* (1977), Giordano and Mays (1977), and Bates *et al.* (1978). This implies that there is not a single linear relationship between total soil Cd and plant Cd, but that the relationship is a function of the annual application rate. Hinesly *et al.* (1976, 1977) stress the importance of the role of annual Cd application, as compared to cumulative Cd application, suggesting that only the current year's Cd application is important. In order for this to be the case, the previously applied Cd must be nearly unavailable to the plant.

Presently, we are unable to account for these differences in plant response to annual and/or cumulative application rates of Cd. This causes a dilemma in that limits to soil application based on accumulation of Cd encourage small applications to new areas of land, whereas an annual application limit encourages application to the same land for extended periods of time. The question raised is whether the objectives are to: minimize the fraction of the soil-applied Cd which is taken up by the crop, and thus the amount of Cd exposure from food by the total population; or to limit the amount of Cd ingested by any individual to some acceptable level, thus creating a smaller potential exposure for more people. If a low limit is placed on the total amount of Cd which can be applied to soil, then at some time all available soils will have accumulated that level of Cd. Thus, if there

is no reduction in plant availability of Cd over time, all crops will be at the higher Cd content; thus the exposure of the total population will be increased. Conversely, if a limit is placed on the annual amount of Cd which can be applied to soil, and the same land area is used continually, the Cd content of only a small fraction of all crops is increased. However, the increase in Cd content of certain crops may be unacceptable if the Cd content is dependent upon cumulative loading rather than annual loading.

From the CAST Report (1980) it is apparent that the slope of the crop response curve to added soil Cd can be different for annual and cumulative Cd additions (i.e., in the case of corn leaves it varied from 0.20 for annual to 0.09 for cumulative). Thus, for a given plant concentration the use of a cumulative response curve would allow for greater application of Cd than an annual response curve. It is apparent that the response curve utilized must be chosen carefully and it would be judicious to use an annual response curve. This would underestimate the cumulative amount of Cd necessary to produce a specific crop level and thus overestimate human exposure.

The choice of crops to be grown on sites where Cd has been added to the soil ranges from leafy vegetables to forages for cattle consumption. From Table 13, it can be seen that the response to annual soil Cd varies from a slope of 0.009 for sweet corn to a slope of 0.60 for lettuce, under neutral soil conditions. Thus, the choice of crop will alter the amount of Cd which can be added by a factor of 60.

TABLE 13
RELATIONSHIP OF CADMIUM IN EDIBLE CROP TISSUE WITH QUANTITY OF CADMIUM APPLIED FOR VARIOUS CROPS

Crop	pH	Slope[a]	Correlation coefficient	Reference
Tomato	6.2–6.5	0.05	0.76	Dowdy and Larson (1975)
Lettuce	6.2–6.5	0.60	0.99	Dowdy and Larson (1975)
	5.5–5.7	0.42	0.77	CAST Report (1980), Table 15
	6.1–6.4	0.15	0.97	CAST Report (1980), Table 15
Swiss chard	5.5–5.7	0.85	0.90	CAST Report (1980), Table 15
	6.1–6.4	0.43	0.96	CAST Report (1980), Table 15
	[b]	0.51	0.94	Chang *et al.* (1978)
Carrot	6.2–6.5	0.20	0.97	Dowdy and Larson (1975)
Radish	6.2–6.5	0.05	0.96	Dowdy and Larson (1975)
	[b]	0.02	0.94	Chang *et al.* (1978)
Potato	6.2–6.5	0.03	0.88	Dowdy and Larson (1975)
Sweet Corn	6.2–6.5	0.009	0.96	Dowdy and Larson (1975)
	5.0–5.5	0.08	0.88	Giordano and Mays (1977)
Stringbean	5.0–5.5	0.01	0.87	Giordano and Mays (1977)
Wheat	[b]	0.02	0.85	Sabey and Hart (1975)
Oats	5.5–5.7	0.02	0.79	CAST Report (1980), Table 15
	6.1–6.4	0.01	0.95	CAST Report (1980), Table 15
Field corn	4.9–5.4	0.001	0.98	CAST Report (1980), Table 17
	5.8–6.4	0.001	0.94	CAST Report (1980), Table 17

[a] x = kg of Cd applied/ha; y = mg of Cd/kg of plant tissue.
[b] Assumed to be >pH 7.

For example, if an increase in Cd composition of food by 1.2 μg/g was acceptable, then only 2 kg/ha of Cd could be added to soils which produce lettuce, whereas 133 kg/ha of Cd could be added to soils which produce sweet corn.

Relationship between Crop Response and Diet

The development of the relationship between Cd ingestion (μg/day) and Cd added to soil (kg/ha) requires that the diet be integrated into a single response curve. The approach used by Pahren *et al.* (1979) assumed that all the food classes which are impacted respond equally. The response curve utilized by the Pahren procedure was that of the most sensitive crop (crops which exhibited the greatest increase in Cd content per unit of Cd applied to soil) in the diet. This approach can logically be extended to an integration of the sensitive crops within the various food classes based on their contribution to the total diet. In order to develop the integrated response curve, a crop response curve for each food class must be selected and the slopes combined on the basis of contribution of each food class to the total diet. The best approach would be to break the diet apart on the basis of crops and do separate response curves for each crop and combine the response curves on the basis of contribution to the diet. This presently cannot be done due to the lack of complete data on crop response and the impact of crop variety on the response curve.

Using the Pahren *et al.* (1979) method, the level of Cd in the diet is adjusted by a multiplication factor

$$\mathrm{MF} = (X_1 - Y)/(X - Y)$$

where

X_1 = projected μg/day of Cd in the diet,
X = μg/day of Cd presently in the diet,
Y = μg/day of Cd in the food classes which are not impacted by addition of Cd to the soil.

This multiplication factor is then used to alter the Cd content of the various food classes (Table 12) in order to obtain the contribution of each food class so that the total equals the projected level. The Cd concentration in food classes is calculated and the amount of Cd which can be added to the soil is obtained from the response curve for a crop from the food classes selected.

For example, if X_1 = 100 μg/day and X = 28 μg/day (Table 12) and all food classes which can be impacted are increased, Y = 8.5 μg/day (for dairy products; meat, fish, poultry; sugars and adjuncts; and beverages, Cd contents are not changed). Then MF = 91.5/19.5 = 4.69. This multiplication factor is then used to increase the amount of Cd in the various food classes and a new concentration for each food class is obtained. Leafy vegetables constitute 1.7 μg Cd/day or a concentration of 40.5 ppb wet wt. Lettuce is 95%, moisture (Watt and Merrill, 1963). Thus, at 40.5 ppb wet wt lettuce contains 0.81 ppm Cd on a dry weight basis. The allowable Cd concentration in lettuce for the 100 μg Cd/day diet would be 3.79 ppm (4.69 × 0.81). Using the lettuce response curve of Dowdy and Larson (1975) (Table 13) and the intercept of 0.81 ppm, the amount of soil-applied Cd which is

necessary to produce a lettuce crop containing 3.79 ppm is 4.96 kg Cd/ha. In contrast, the allowable Cd concentration in grain for the 100 μg Cd/day diet would be 0.17 ppm (4.69 × .035). Using the response curve for wheat of Sabey and Hart (1975) (Table 13), the amount of soil-applied Cd which is necessary to produce a wheat crop concentration of 0.17 ppm is 6.75 kg Cd/ha. It becomes apparent that the selection of food class and the response curve to represent the food class affects the amount of Cd necessary to reach a predetermined increase in the diet.

Carrying out this procedure for other values of daily Cd ingestion, a curve relating daily Cd ingestion and kilograms per hectare of Cd added can be developed (Fig. 2). This relationship can also be developed for the lacto-ovo-vegetarian diet and for acid soils as well as neutral soils (Fig. 2). From Table 13 it is apparent that a change in pH from the range of 6.1−6.4 to 5.5−5.7 causes an increase in the slope by a factor of 2 for swiss chard and 3 for lettuce. The factor 3 was utilized to represent an acid soil system.

In order to obtain a more realistic relationship between Cd ingestion and soil Cd, an integrated response curve for the grain, leafy vegetables, legume vegetables, garden fruits, potatoes, and root vegetables was obtained. This was done by using the response curves for the more sensitive crops within each of these food classes and by combining these on the basis of their contribution to the total diet to form a single response curve. For example, the leafy vegetable food class makes up 6.40% of the impacted food classes within the normal diet. Therefore, the lettuce accounts for 6.40% of the integrated response curve. Percentages and crop response curves for the other food classes were obtained and an integrated crop response model was developed. In order to convert the food class concentration from a wet weight basis to a dry weight basis the percentage moisture for each

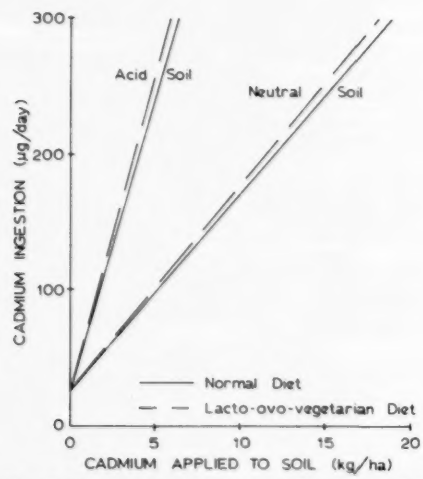

FIG. 2. Effect of soil pH and diet preference using nonintegrated model. Assumes that all food classes except dairy products; meat, fish and poultry; beverages; and sugars and adjuncts are impacted and that all food classes respond as does lettuce.

class was calculated utilizing FDA Compliance Program Evaluation (1974) and Watt and Merrill (1963). This response curve was then used, as above, to develop the relationship between Cd ingestion and kilograms per hectare of Cd added for the lacto-ovo-vegetarian and normal diet under neutral soil conditions (Fig. 3).

As stated, the above relationships between Cd ingestion and Cd application rates assume that an individual's entire diet is produced on amended soils. As a result of the food production and distribution system in the United States, this seems to be an unlikely situation except for the case of the home garden. Kaitz (1978) found that 46% of the 33 $\times$ 10^6 households in the United States had a garden. Assuming that households translate to population, 46% of the population produces some of its own food. Eight percent of the households with gardens had garden plots larger than 0.2 ha (0.5 acres). Assuming that a garden of larger than 0.2 ha (0.5 acres) is necessary to produce all one's food, only 3.7% of the population can be so categorized. A maximal impact of Cd could only apply to this 3.7% of the population.

In order to further expand the population covered, it can be assumed that only the food grain crops are produced on Cd-amended soils. Again it is assumed that all of these crops are produced on Cd-amended soils and thus the individual is obtaining all his grain and grain products from amended sites.

Curves for daily Cd ingestion vs Cd added to the soil (Fig. 4) were developed by using the response curve for wheat (Table 13). As anticipated, much greater Cd additions are required for a given level in the diet. It must be remembered that for this situation the assumption that all grain crops are impacted is conservative. The total amount of Cd-containing sewage sludge available for land application is

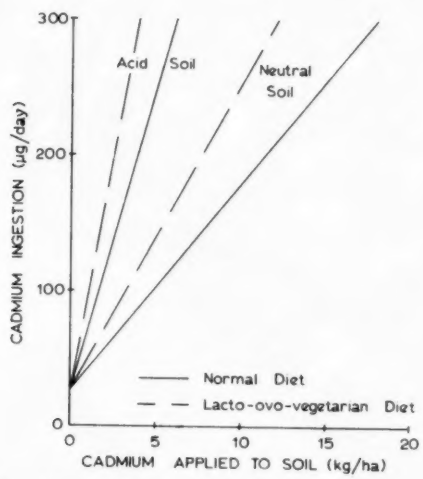

FIG. 3. Effect of soil pH and diet preference using integrated model. Assumes that grain and cereal products, potatoes, leafy vegetables, legume vegetables, and garden fruits are impacted and that they respond as does the most sensitive crop within each food class.

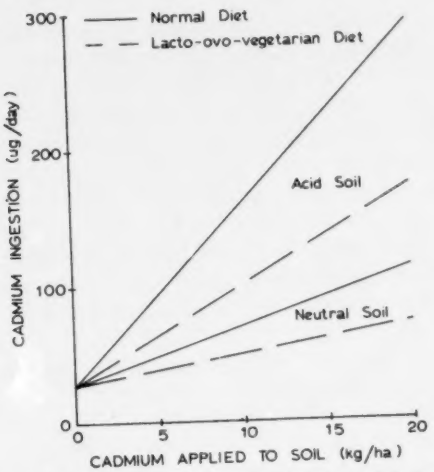

FIG. 4. Effect of soil pH and diet preference using food grain model. Assumes that only the grain and cereal products food class is impacted and that it responds as does wheat.

limited. Another factor is the degree of dilution that can occur during grain transportation, storage, and processing.

The degree of mixing of food products before consumption is important. In the CAST Report (1976) the metal ingested by each person was computed by assuming that all grains (from sludge-amended soils and control) were completely mixed before ingestion. At the other extreme, it might be assumed that no mixing occurs, resulting in a higher ingestion of Cd by the population consuming the food and no increase by the rest of the population.

The effects of diet dilution can be computed as follows: The extent of mixing can be expressed as a dilution factor D defined as the total amount of food produced divided by the amount of food produced on amended soils. The inverse of D would be the fraction of the food produced on Cd-amended soil. For example, 1976 corn production was 158×10^6 metric tons with an average yield of 5.5 metric tons/ha with 2.8×10^6 ha being harvested. In 1970, municipal treatment plant sludge production was estimated as 3.6×10^6 metric tons with an average concentration of 20 ppm Cd (CAST, 1976). Thus, the maximum amount of Cd potentially available for farm land was 72,000 kg. If the loading rate was 2 kg/ha, a total of 36,000 ha would be used. Thus, 198,000 metric tons of Cd-impacted grain would be produced. The dilution factor D would be 798 (i.e., $158 \times 10^6/198 \times 10^3$), which equals 0.13% of all corn grown.

In contrast, the Versar Report (EPA, 1975a) and the Stanford Research Report (EPA, 1977) estimate that municipal sewage sludge contains 300,000 and 367,000 kg of Cd, respectively. Using the 367,000 kg number and the 2 kg/ha loading rate the dilution factor would be 158 (i.e., $158 \times 10^6/1.0 \times 10^6$), or 0.63%.

Another form of diet dilution occurs when crops are used to feed animals later used for human food. Numerous investigators have studied the effects of elevated

Cd intake on the Cd concentration of muscle tissue of experimental animals: Sharma *et al.* (1979); Hansen and Hinesly (1979); Bertrand *et al.* (1978); Edds and Davidson (1981); University of Florida (1978); Furr *et al.* (1976); Kienholz *et al.* (1976, 1979); Baxter *et al.* (1976). All agree that Cd does not seek muscle tissue and no significant differences are found between experimental animals and control animals. The lack of impact on animal muscle tissue is true whether the animals graze on grasses grown on sludge-amended soil, or are given a pure Cd compound in their food. In contrast, Leach *et al.* (1979), in their study with chickens, and Doyle *et al.* (1974), in their study with lambs, found an increase in animal muscle Cd concentration with increasing doses of Cd and that the effect is significant at elevated levels of Cd in the diet (i.e., 48 and 60 μg Cd/g of feed, respectively). This elevation may simply reflect elevated blood Cd levels. It appears there should be little concern about Cd with nonvisceral meats in the marketplace, unless very high levels of Cd are in the animals diet.

Calculations, based on the U.S. Department of Agriculture survey of the American diet, indicate that liver constitutes 1.5% of the meat, fish, and poultry food class total. Kidneys form a negligible part of the human diet, but may be used in the manufacture of processed meat and poultry products.

A number of studies have been made in recent years comparing liver Cd in cattle exposed directly or indirectly to municipal sludge. Multiples of the control level found were 2.37 (Fitzgerald, 1978), 1.75 (Baxter *et al.*, 1976), 1.43 (Bertrand *et al.*, 1978), 1.04 (Edds and Davidson, 1981), and 2.58 (University of Florida, 1978). The average of the multiples was 1.83.

Cadmium levels in livers of animals without known Cd exposure, other than normal foods, may be calculated from the control animals used in these studies. Values found were 0.20 ppm (Sharma *et al.*, 1979), 0.14 (Bertrand *et al.*, 1978), 0.27 (Edds and Davidson, 1981), 0.20 (University of Florida, 1978), 0.80 (Baxter *et al.*, 1976), 0.79 (Fitzgerald, 1978), and 0.06 ppm (Munshower, 1977), with an average of 0.35 ppm.

The actual impact of exposing animals to Cd-bearing sludge via their feed can be calculated. The FDA market basket survey for 1974 showed the concentration and average intake for the meat, fish, and poultry food class to be 0.015 ppm and 3.1 μg/day, respectively (Compliance Program Evaluation, 1974). The nonliver portion of the food class may be calculated as

$$(0.35 \text{ ppm})\,(0.015) + \left[(X \text{ ppm})\,(0.985)\right] = (0.015)\,(1.0),$$

where each set of values represents the liver portion, the nonliver portion, and the total respectively.

The 0.015 figure is the liver fraction of the American diet. The concentration of the nonliver portion is 0.010 ppm. Liver fully impacted by Cd would have a concentration of $0.35 \times 1.83 = 0.64$ ppm.

$$(0.64 \text{ ppm})\,(0.015) + \left[(0.01 \text{ ppm})\,(0.985)\right] = (X \text{ ppm})\,(1.0),$$

where $X = 0.019$ ppm for the meat food class. With the meat food class averaging 204 g/day, the Cd intake would be

$$204 \text{ g/day} \times 0.019 \ \mu\text{g/g} = 3.87 \ \mu\text{g/day}.$$

From Table 12 the total Cd intake from all food classes would be 28 μg/day. The maximum increase in the total diet would be

$$(3.87 - 3.1)/28 \times 100 = 2.8\%.$$

If all cattle consumed in the United States were not impacted by sludge, the increase would be proportionately less. For example, of the 43.2×10^6 ha of feed grain grown in the United States in 1976 (Agriculture Statistics, 1977), only 367,000 ha could be impacted at 1 kg Cd/ha if all the municipal sludge produced were used to grow animal grains. Therefore, a maximum of 0.85% of the cattle could be impacted by sludge. Assuming these livers would be mixed with those not impacted by sludge through the marketing process, the increase in the total diet would be 0.023% and thus insignificant.

Because the average diet includes only limited amounts of liver, consideration of this food should be given only for those consuming it in large amounts.

Calculation of Sludge-Loading Rates

Utilization of the data from each set of assumptions requires that a level of Cd exposure be chosen which would not be exceeded. From Figs. 2, 3, and 4 a corresponding level of annual application based on various management requirements can be obtained. For example, assuming an acceptable exposure of 100 μg Cd/day, and no controls required other than a Cd-loading limit, then an individual who used the material as a fertilizer for a garden where he obtained his total diet (excluding meat, dairy products, beverages, and sugar and adjuncts) would not exceed 100 μg Cd/day ingestion if he limited the Cd to 1.7 kg/ha under acid soil conditions. Using the same exposure limit and assuming a neutral pH requirement as well as a Cd application limit, then 5.0 kg Cd/ha could be applied, where lettuce is used to predict diet response. If, however, the six food classes (grain, potatoes, leafy vegetables, legume vegetables, root vegetables, and garden fruit) are allowed to respond independently, but using the more sensitive crop within each class, 4.8 kg Cd/ha could be applied. Using the same exposure limit, assuming a neutral pH and a requirement that only agriculture grain crops be grown on the site, then the Cd application limit becomes 17 kg/ha. This procedure was utilized for ingestion limits of 440, 200, 100, and 50 μg Cd/day to develop Table 14, which illustrates the impact of ingestion limit and management practice on the Cd application limit.

To calculate the maximum percentage of the population which could be impacted by various loading rates it was assumed that: there was no dilution of the crops grown on Cd-amended soils; there were 367,000 kg Cd in sewage sludge; there were 2.5×10^6 ha of land used for gardens, or 30×10^6 ha of land used to produce food grain crops; and 46% of the population had gardens. Where an individual used the material to produce his entire diet, the percentage of population impacted equals (0.46) (kg Cd ÷ kg Cd/ha loading rate) ÷ total ha of land. The 0.46 was not used in the calculations where an individual used the material to produce food grain crops. These calculations were carried out for Cd-loading rates of 0.5 to 10 kg/ha (Table 15). Additionally, the percentage of the impacted popula-

TABLE 14
APPLICATION RATES (kg/ha) OF CADMIUM FOR VARIOUS INGESTION LIMITS AND AGRICULTURE MANAGEMENT SYSTEMS

Exposure limit (μg Cd/day ingested)	Scenario 1[a]					Scenario 2[b]	
	Neutral soil				Acid soil	Neutral soil	
	Lacto-ovo-vegetarian diet		Normal diet		Normal diet	Lacto-ovo-vegetarian diet	Normal diet
	A	B	A	B	A		
440	27.4	18.5	28.5	24.9	9.5	169	96
200[c]	11.5	7.8	11.9	11.5	4.0	71	40
100[d]	4.9	3.3	5.0	4.8	1.7	30	17
50	1.5	1.5	1.5	1.5	0.5	8.9	4.9

[a] Scenario 1 assumes that all the food classes are produced on cadmium-amended soils and uses lettuce as a crop response model for A and the integrated response curve for the more sensitive crops in the six food classes for B.

[b] Scenario 2 assumes that only food grains are produced on cadmium-amended soils with a neutral pH and uses wheat as a crop response model.

[c] Ingestion of 200 μg/day of cadmium over a 50-year period is a reasonable estimate of the amount of cadmium ingestion necessary for most sensitive (excluding smokers and occupationally exposed) individuals within the population to reach the critical body burden (200 μg Cd/g wet wt in the renal cortex).

[d] Ingestion of 100 μg/day of cadmium over a 45-year period would be expected to result in a measurable incidence of β_2-microglobulinuria according to the Kjellström model.

tion which is expected to be at risk (200 μg Cd/g in renal cortex), as projected by the ingestion limit approach and the Kjellström model, is indicated in Table 15.

From Table 15 it can be seen that the higher the loading rate, the smaller the population which can be impacted, but the greater the risk to the impacted population. The amount of dilution which occurs because of the marketing process would reduce the risk considerably.

The requirement that all municipal sludge be used to grow grain for animal feed would eliminate the need for a Cd soil limit to protect public health. In reality, not all sludge is applied to the surface of the land. Probably no more than 50% of the total would be utilized. Therefore, on the average, the maximum population-exposed values in Table 15 could be divided by two. The increase in the total diet due to consumption of livers impacted by sludge would also be divided by two, thereby not exceeding 0.012%. There would be no reason to condemn such livers as a routine measure.

From Tables 14 and 15 it becomes apparent that the major factors controlling Cd content of crops, and thus ingestion, are soil pH and amount of Cd applied to the soil. Maintaining a neutral soil pH at a land application site would mean utilizing higher loading rates and less land. For example, assuming an ingestion limit of 100 μg Cd/day and using Scenario 1, 1.7 and 5.0 kg Cd/ha can be applied for the acid and neutral soils, respectively. The risk to the individual would be the same, but

TABLE 15

EFFECT OF CADMIUM LIMIT ON PERCENTAGE OF TOTAL POPULATION EXPOSED AND PERCENTAGE OF EXPOSED POPULATION PROJECTED TO REACH 200 μg Cd/g IN THE RENAL CORTEX AFTER 50 YEARS EXPOSURE BY KJELLSTRÖM MODEL OR AN INGESTION LIMIT

	Scenario 1[a]							Scenario 2[b]		
		Kjellström model			Ingestion limit[d]					
Cadmium limit (kg/ha)	Maximum[c] population exposed	Acid	Neutral		Acid	Neutral		Maximum[e] population exposed	Kjellström model neutral	Ingestion limit neutral
			A	B		A	B			
10	0.68	52	15[f]	26[f]	100	0	100[f]	0.12	1.8	0
5	1.35	22	4[f]	9[f]	100	0	0	0.24	0.6	0
4	1.69	19	3[f]	6[f]	100	0	0	0.31	0.4	0
3	2.25	12	2	4[f]	0	0	0	0.41	0.3	0
2	3.38	6	1	1.8[f]	0	0	0	0.61	0.2	0
1	6.75[g]	1.8	0.3	0.6[f]	0	0	0	1.22	0.15	0
0.5	14.24[g]	0.6	0.2	0.3[f]	0	0	0	2.45	0.1	0

[a] Scenario 1 assumes that all the food is produced on cadmium-amended soils and uses lettuce as the crop response model for A and the integrated response curve for the more sensitive crops in the six food classes for B.

[b] Scenario 2 assumes that only food grain crops are produced on cadmium-amended soils with a neutral pH and uses wheat as the crop response model.

[c] Population exposed calculation is based on ha of land required for application of 367,000 kg of cadmium at specified rate as percentage of the 2.5×10^8 ha used to produce home gardens times 0.46 (percent of households with gardens).

[d] Ingestion limit assumes that an ingestion of 200 μg/day of cadmium over a 50-year exposure period is a reasonable estimate of the amount of cadmium ingestion necessary for the more sensitive (excluding smokers and occupationally exposed) individuals within a population to reach 200 μg Cd/g in renal cortex.

[e] Population exposed calculation is based on ha of land required for application of 367,000 kg of cadmium at specified rate as percentage of 30×10^6 ha used to produce 1976 food grain crop.

[f] Percentages represent the more sensitive vegetarian diet.

[g] Percentages would be lower because only 3.7% of the population could raise all their own food (excluding meat and dairy products).

for the acid soil three times as much land would be required, and three times as many people would be at risk.

A requirement for neutral pH can be made. For large areas of the United States (northeast and southeast), however, it would be extremely difficult to maintain. The pH must be kept at the required level while the land is being utilized for sludge. Once application is stopped, there will need to be a mechanism for assuring that pH is not allowed to decrease. If this decrease does occur, there would be a need to prevent the soil being used for raising crops which would increase health risks.

It is also apparent that as requirements are increased (soil, pH, crop, animal, etc.) the rate of application can be increased and, thus, the potential number of people impacted decreased. This leads to a debate on the concept of controlled land application sites with fewer people impacted versus general agriculture utilization of the sewage sludge with a larger segment of the population impacted.

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